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<b>(21) International Application Number:</b> PCT/US93/08714 <b>(22) International Filing Date:</b> 14 September 1993 (14.09.93) <b>(30) Priority data:</b> 07/943,169 14 September 1992 (14.09.92) US <b>(71) Applicant:</b> RUTGERS, THE STATE UNIVERSITY OF NEW JERSEY [US/US]; Old Queens Building, Somerset and George Streets, New Brunswick, NJ 08903 (US). <b>(72) Inventors:</b> CHIEN, Yie, W. ; 5 West Lake Court, North Brunswick, NJ 08902 (US). CHEN, Guo-Shen ; No. 5 Huang Gu Shan Street, Hang Zhou, Zhejiang (CN). CHIEN, Te-Yen ; 10 Quail Court, Branchburg, NJ 08876 (US).		<b>(74) Agent:</b> SINN, Leroy, G.; P.O. Box 559, Oldwick, NJ 08858 (US). <b>(81) Designated States:</b> AU, CA, FI, JP, KP, KR, NO, NZ, PL, RU, UA, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> TRANSDERMAL CONTROLLED DELIVERY OF PHARMACEUTICALS AT VARIABLE DOSAGE RATES AND PROCESSES  <b>(57) Abstract</b> <p>Transdermal polymer dosage units are provided which comprise a backing layer and a reservoir layer. The reservoir layer can have multiple regions which contact the skin during use, optionally may have different pharmaceuticals, may provide variable rate of transdermal absorption, and may provide the pharmaceuticals in the form of microreservoirs or one or more macroreservoirs. The reservoir region can comprise a macroreservoir of one or more pharmaceuticals wherein the reservoir is bounded by a backing layer and a layer of a substantially non-porous permeability-regulating polymer membrane which directly or indirectly contacts the skin during transdermal administration. Also, provided is a process of transdermal administration of pharmaceuticals using the novel dosage units.</p>		

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5                   TRANSDERMAL CONTROLLED DELIVERY OF PHARMACEUTICALS  
                    AT VARIABLE DOSAGE RATES AND PROCESSES

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TECHNICAL FIELD

20                   A novel transdermal absorption dosage unit by which  
multiple pharmaceuticals can be provided for transdermal  
25                   absorption simultaneously at different or variable dosage  
rates and at relatively constant permeation profiles. The  
dosage units can provide the desired differences or varia-  
30                   tion in the dosage rates by providing multiregional areas of  
the dosage unit which have different compositions with  
respect to the pharmaceuticals. The novel dosage units of  
35                   this invention can also provide controlled and variable  
dosage rates of two or more pharmaceuticals on a simul-  
40                   taneous basis from a single reservoir area. A single dosage  
area can comprise a reservoir in which the pharmaceuticals  
are in liquid state and are contained by a permeability-  
45                   regulating membrane, which can come in contact either  
directly or indirectly with the skin of the subject being  
50                   treated. The pharmaceuticals administered by the dosage  
unit of this invention can vary widely. Additionally, this  
invention relates to an improved process for transdermal  
55                   systemic delivery of pharmaceuticals.

BACKGROUND ART

It has been found that certain pharmaceuticals are absorbed to a degree through the skin. This is referred to as transdermal absorption. One means of transdermal absorption has been to disperse the pharmaceutical within a polymeric disc or a container of a gel and then contacting an area of the skin of the subject to be treated with the disc or gel containing the pharmaceutical. Problems encountered in the past include adequate control over the rate and duration of transdermal absorption or the rate can be too slow in the case of certain dosage forms, especially from pharmaceutical-containing discs or pharmaceutical-containing gel container dosage units. It has been found that the transdermal absorption rates of certain pharmaceuticals can be increased by coadministering one or more transdermal absorption-enhancing agents with the pharmaceutical to be absorbed when compounding the polymeric disc or the pharmaceutical-containing gel.

It is desired to improve the dosage unit forms or devices by which pharmaceuticals are transdermally absorbed, especially in view of the importance of administering pharmaceuticals by this means. Desired transdermal absorption of pharmaceuticals would provide an avoidance of gastrointestinal incompatibility with the pharmaceuticals and unwanted destruction of the pharmaceuticals by metabolism in the gastrointestinal tract and by a hepatic "first-pass" metabolism. The transdermal absorption minimizes inter- and

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10 intra-patient variations regarding such incompatibilities  
and metabolisms. By transdermal absorption, it is deemed  
possible to provide a more constant pharmaceutical concen-  
15 tration in the body and to realize a greater pharmacological  
efficacy. It is possible, by proper transdermal absorption,  
to reduce the frequency of dosing. Transdermal administra-  
20 tion provides most of the advantages of intravenous dosing  
without the necessity of hospitalization and the accompany-  
ing discomfort and inconvenience.

25 It is desired to improve the administration by trans-  
dermal means of pharmaceuticals by modulating the delivery  
of pharmaceuticals, desirably at substantially constant  
30 rates. It is also desired to administer two or more phar-  
maceuticals with synergistic therapeutic activities, simul-  
35 taneously, especially at variable dosage rates. For  
example, it is often desired in regulating fertility by  
administering simultaneously an estrogenic steroid, such as  
40 17-beta-estradiol (commonly referred to as "estradiol"), and  
also to administer simultaneously a progestational steroid.  
45 These hormonal steroids normally have differing absorption  
rates and require different dosage amounts of the respective  
steroids. These steroids are used for either fertility  
50 regulation or for the treatment of postmenopausal syndrome  
and other hormonal replacement therapy.

5           It is desired to provide such improved dosage units  
which enable controlled delivery of pharmaceuticals,  
10       including steroidal hormones, with the possibility of two or  
more pharmaceuticals being administered simultaneously at  
controlled and variable dosage rates. Furthermore, it is  
15       desired to provide improved methods of administration of  
pharmaceuticals, including the simultaneous administration  
20       of multiple pharmaceuticals with different pharmacological  
activities, including hormonal activities, to achieve a  
synergistic effect.  
25

#### SUMMARY OF INVENTION

30           This invention relates to a transdermal dosage unit for  
administration of one or more pharmaceuticals simultaneously  
at controlled and variable rates of transdermal delivery.  
35       The transdermal dosage unit provided by this invention com-  
prises the following:

- 40       a) a backing layer which is impervious to the ingredients  
of the dosage unit;
- 45       b) a reservoir having present for transdermal absorption  
one or more pharmaceuticals, said multiple pharmaceuti-  
cals being compatible and being delivered simultaneous-  
50       ly, preferably at constant rates of administration,  
over a predetermined duration of administration;
- 55       c) means which desirably provide variable transdermal  
absorption rates of the one or multiple pharmaceuticals  
in an effective amount to result in substantially con-

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stant systemic levels continuously for at least 24 hours; and

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- d) an adhesive means to affix said dosage unit to the intact skin of a subject receiving the therapy provided thereby.

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The reservoir can be provided in multiregions, which are in contact with the skin of the subject undergoing treatment with said dosage unit, at least two of which provide transdermal absorption of one or more pharmaceuticals simultaneously from each of the regions.

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The dosage unit permits two or more pharmaceuticals to be administered transdermally and simultaneously through the intact skin to achieve therapeutically effective systemic concentrations and to maintain the therapeutic concentrations at substantially constant levels continuously for at least a 24-hour period. Pharmaceuticals which are subject to hepatic "first-pass" elimination or which are irritating to the gastrointestinal tract and which have synergistic or additive effect when used in combination can be selected for administration by the dosage units of this invention. One of the combinations of pharmaceuticals which can be administered by the dosage units of this invention is a combination of progestational and estrogenic steroids, natural or synthetic, for the regulation of fertility or treatment of post-menopausal syndrome or other hormonal steroid therapy. Other possible combinations of pharmaceuticals which can

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be administered by the dosage units include: (1) testosterone and 17-methyl testosterone, (2) testosterone and estradiol, (3) AZT and DDC (or DDI), (4) a propranolol and hydrochlorothiazide, (5) bumetanide and cyclothiazide. The reservoir can comprise mono- or multi-regional reservoir compartments which are adapted to provide controlled and variable delivery of two or more pharmaceuticals on a simultaneous basis and at rates which are substantially constant continuously for a period of at least 24 hours or longer. The mono- or multi-regional pharmaceutical reservoir compartment or compartments can be provided by forming the reservoir between two sheets of pharmaceutical-impermeable protective plastic laminates: the one laminate layer comprising a peelable release liner to be removed just before application of the dosage unit to the subject of the therapy and another layer being a backing layer to house and to protect the pharmaceutical reservoir compartments from the environment as well as to control and to restrict the pharmaceuticals to be delivered transdermally to the skin of the subject being treated.

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The rate of transdermal delivery can be achieved by controlling the solubility of the respective pharmaceutical or pharmaceuticals and the permeability across a permeability-regulating membrane and the skin. The rates of transdermal permeation can be programmed at therapeutically-effective ratios. The solubility of the one or more pharma-

5           ceuticals administered from said dosage unit as stated above  
10           can be provided from a single reservoir area or from mul-  
15           tiple reservoir areas of the transdermal dosage unit pro-  
            vided hereby by changing, regulating or varying the rate of  
            transdermal permeation.

20           In providing the preferred dosage units of this inven-  
25           tion, it is useful and necessary to study the differences in  
30           solubility and permeability of the one or more pharmaceuti-  
            cals to be coadministered by the application of the dosage  
            units of this invention, whether they are mono- or multi-  
            regional drug reservoir compartment dosage units whereby the  
            one or more pharmaceuticals can be delivered transdermally  
            at variable dosage rates to achieve desired therapeutically-  
            effective ratio or ratios.

35           If a multiregional reservoir is used, it is desirable  
            that at least one region has at least one pharmaceutical  
            present in the form of a macroreservoir or microreservoirs.

40           If a macroreservoir form is used, it is desired that  
45           the macroreservoir be covered by application to the pharma-  
            ceutical-releasing surface of the reservoir a permeability-  
50           regulating polymeric membrane, which is non-porous. If  
            microreservoirs are used, the preferred non-porous per-  
55           meability-regulating membrane is a (ethylene/vinyl acetate)  
            copolymer wherein the vinyl acetate content can be in the  
            range (by mean weight) of about 4.6 percent to about 50  
            percent; presently preferred in the mean weight range from  
            about 18 to about 40 percent.

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It is also presently preferred that the rate of one or more of the pharmaceuticals provided by the dosage unit can be made variable, for example, by using a combination of mutually miscible, bioacceptable solvents. It has been found suitable to use, for example, certain mutually miscible, bioacceptable water-organic solvent combinations, such as certain water-ethyl alcohol combinations. It has been found preferable, for example, in simultaneous transdermal systemic delivery of an estrogen, such as estradiol, and a progestin, such as levonorgestrel, to use a water-ethyl alcohol combination wherein the content (by volume) of ethyl alcohol is about 40 to about 85 percent based on the combined volume of water and ethyl alcohol.

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If at least one pharmaceutical is to be present in the reservoir in the form of microreservoirs of the pharmaceutical, the pharmaceutical can be dissolved in a biocompatible liquid which can provide variability of the transdermal absorption rate if desired. For example, combinations of water and polyethylene glycol or the like can be used. The pharmaceutical can be dispersed and dissolved in liquid before dispersion into a biocompatible polymeric material, such as an adhesive polymer, elastomeric polymer or gelling polymer and then stirred at sufficiently high speed to form a pharmaceutical-containing polymeric material wherein microreservoirs of the dissolved pharmaceutical are dispersed in a polymeric material. The polymer selected must

5 be biocompatible, compatible with the pharmaceuticals micro-  
dispersed therein and permit the release of the pharmaceuti-  
10 cals for the desired transdermal absorption.

Provided hereby also is a novel method of transdermal  
absorption of pharmaceuticals using the transdermal dosage  
15 units of this invention.

#### 20 BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows a dosage unit of this invention, wherein  
the reservoir for the pharmaceuticals contains two pharma-  
25 ceuticals, A and B, in a macroreservoir form. The macro-  
reservoir is covered by a pharmaceutical permeability-regu-  
lating polymer membrane. The dosage unit is shown as a  
30 cross-sectional view. The dosage unit has a pressure sensi-  
tive adhesive polymeric ring in a peripheral location with  
respect to the macroreservoir containing pharmaceuticals A  
and B. Shown as FIG. 1-(A) is a top view of the dosage unit  
40 of FIG. 1.

FIG. 2 shows a dosage unit of this invention similar to  
that shown in FIG. 1 and FIG. 1-(A) with the exception that  
45 the peripheral ring is made of a polymeric adhesive material  
and comprises a microreservoir containing pharmaceutical B.  
The central compartment A consists of a macroreservoir con-  
50 taining pharmaceutical A. FIG. 2-(A) represents a top view  
of the dosage unit of FIG. 2 shown in cross-sectional view.  
55

5           FIGS. 3A and 3B show the permeation profile of levo-  
norgestrel as it is varied, depending upon the amount of  
10 ethanol present in a water-ethanol combination as compared  
to 100% water and 100% ethanol.

15           FIG. 4 shows the variation in the skin permeation rate  
of levonorgestrel dependent upon the concentration of etha-  
nol in water on a volume/volume percent basis.

20           FIG. 5 is a graph showing the difference in levonorges-  
trel permeation rate depending upon the weight percent of  
25 vinyl acetate in the permeability-regulating (ethylene/vinyl  
acetate) copolymer membrane in a dosage unit as shown in  
FIG. 1 and 2.

30           FIG. 6 is a graph showing the effect of the vinyl ace-  
tate content in the permeability-regulating membrane con-  
sisting of a (ethylene/vinyl acetate) copolymer upon the  
35 permeation rate of levonorgestrel across hairless rat skin.

40           FIG. 7 is a graph which shows the difference in the  
skin permeation profile of levonorgestrel vs. the thickness  
of a permeation-regulating (ethylene/vinyl acetate) copoly-  
mer membrane in a dosage unit of the type shown in FIGS. 1  
45 and 2 as compared with the permeation rate wherein no mem-  
brane is in contact with the skin.

50           FIG. 8 is a graph which shows the relationship between the  
skin permeation rate of levonorgestrel across the per-  
meability-regulating membrane utilizing a (ethylene/vinyl  
55 acetate) copolymer membrane containing 28% vinyl acetate and  
wherein the macroreservoir solution contains 70% ethanol, as

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10 solubilizer, 2% oleic acid, as skin permeation-enhancing agent, and 28% water on a volume/volume basis. The dosage unit utilized in this evaluation is of the type shown in FIGS. 1 and 2.

15 FIG. 9 is a graph which shows the skin permeation rate of levonorgestrel (in  $\text{mcg}/\text{cm}^2/\text{hr}$ ) from a macroreservoir solution containing varying ratios of ethanol and water on a  
20 v/v basis and also shows how the absorption is affected by the presence of five percent of two different skin permea-  
25 tion-enhancing agents. The dosage unit utilized in this evaluation is of the type shown in FIGS. 1 and 2.

30 FIG. 10 is a graph which shows the change in skin permeation rate of levonorgestrel from a saturated levonorgestrel reservoir solution having a 70:30 ethanol:water ratio  
35 on a V/V basis. The dosage unit used is of the type shown in FIGS. 1 and 2. The vinyl acetate content in the permeability-controlling (ethylene/vinyl acetate) copolymer  
40 membrane is 28% and the thickness of the membrane is 50 microns. The rate of permeation is shown to increase as the  
45 concentration of oleic acid (as the skin permeation-enhancing agent) is increased.

50 FIG. 11 is a graph showing the effect of estradiol loading dose on the permeation rate across the hairless rat skin covered with permeability-regulating (ethylene vinyl  
55 acetate) copolymer membrane wherein the vinyl acetate content is 28 percent and the thickness of the membrane is 50

5 microns. Hairless rat skin was utilized in this evaluation.  
The reservoir solution used is a saturated levonorgestrel  
10 solution wherein the ethanol concentration is 70 percent and  
the concentration of oleic acid as the skin permeation-  
enhancing agent is 2 percent. Permeation rates are shown  
15 for estradiol and levonorgestrel, in which permeation rate  
of estradiol varies as a function of the loading dose of  
estradiol in the solution. A dosage unit of the type shown  
20 in FIG. 1 is utilized in this evaluation.

25 FIG. 12 is a graph showing the effect of estradiol  
loading dose on the ratio of skin permeation rates of levo-  
norgestrel over estradiol. In the evaluation, a permeabil-  
ity-regulating (ethylene/vinyl acetate) membrane having a  
30 vinyl acetate content of 28 percent and a thickness of 50  
microns is used. The hairless rat skin test is utilized as  
well as the saturated levonorgestrel concentration in 70  
percent ethanol and 2 percent oleic acid, as the enhancer,  
35 are used.  
40

FIG. 13 is a graph which shows estradiol permeation  
45 profiles from a dosage unit such as the one shown in FIG. 1  
utilizing the test procedure in which human cadaver skin is  
covered with a permeability-regulating (ethylene/vinyl ace-  
50 tate) copolymer membrane. The skin permeation of estradiol  
is from a reservoir solution having levonorgestrel at  
saturation concentration. Various estradiol concentrations  
55 are utilized in the comparative testing, with estradiol  
loadings varying from 0.2 to 10 milligrams/milliliter and to

5 saturation concentration. A dosage unit of the type shown  
10 in FIG. 1 is used.

15 FIG. 14 is a graph which shows a permeation profile of  
levonorgestrel across a permeability-regulating (ethylene/  
vinyl acetate) copolymer membrane covered human cadaver  
20 skin. The dosage unit utilized is of the type shown in FIG.  
1. Varying estradiol concentrations are used in the reser-  
voir solution varying from 0.2 mg/ml to saturation.

25 FIG. 15 is a graph showing the effect of estradiol  
loading in a dosage unit as shown in FIG. 1 on the permea-  
tion rates of estradiol and levonorgestrel across a per-  
meability-controlling membrane utilizing an (ethylene/vinyl  
30 acetate) copolymer membrane. The evaluation is done in the  
absorption test utilizing human skin. The donor solution  
35 contained in the macroreservoir is saturated with levonor-  
gestrel, contains 2 percent oleic acid as an enhancing agent  
and has 70 percent ethanol and 28 percent water.

40 FIG. 16 is a graph showing the effect of estradiol  
loading on the ratio of the permeation rates of levonorges-  
45 trel over estradiol. The permeability-controlling membrane  
of (ethylene/vinyl acetate) copolymer is utilized wherein  
the vinyl acetate content is 28 percent and the thickness is  
50 50 microns. Levonorgestrel is present at saturated condi-  
tion. Two percent oleic acid and 70 percent ethanol are  
55 utilized in the aqueous reservoir solution. Human cadaver  
skin is used in the absorption test.

5           FIG. 17 is a graph showing the effect of variation in  
the ratio the pharmaceutical-releasing area in a dosage unit  
10       of the type shown in FIG. 2 on the dosage rate ratio of  
levonorgestrel/estradiol. Levonorgestrel is present in the  
macroreservoir wherein the reservoir solution is 70 percent  
15       ethanol and 30 percent water. The permeability-controlling  
membrane is a (ethylene vinyl acetate) membrane having 28  
20       percent vinyl acetate and a thickness of 50 microns. Estra-  
diol is present in the peripheral ring reservoir as a micro-  
reservoir of estradiol wherein the polymeric material used  
25       is a polyacrylate.

FIG. 18 shows a dosage unit wherein two distinct reser-  
30       voirs are present, the reservoirs having pharmaceuticals A  
and B, respectively. The reservoirs have the pharmaceuti-  
cals present in a matrix form.

#### 40       DETAILED DESCRIPTION OF THE INVENTION AND THE PREFERRED EMBODIMENTS

The backing layer can be made of any suitable material  
which is impermeable to the pharmaceuticals dispersed within  
45       the adjacent reservoir layer. The backing layer serves as a  
protective cover and provides also a support function. The  
backing can be formed so that it is essentially the same  
50       size layer as the central reservoir containing one or more  
pharmaceuticals or it can be of larger dimension so that it  
55       can extend beyond the side of the central reservoir or over-  
lay the side or sides of the reservoir and then can extend

5           outwardly in a manner that the surface of the extension of  
the backing layer can be a base for a pressure-sensitive  
10       adhesive ring to hold the dosage unit in intimate contact  
with the skin of the subject treated.

15           Examples of materials suitable for making the backing  
layer are films of high and low density polyethylene, poly-  
propylene, polyvinylchloride, polyesters such as poly (ethy-  
20       lene phthalate), metal foils, metal foil laminates of such  
suitable polymer films, and the like. Preferably, the mate-  
25       rials used for the backing layer are laminates of such poly-  
mer films with a metal foil such as aluminum foil. In such  
laminates, a polymer film of the laminate will usually be in  
30       contact with the pharmaceutical-containing reservoir. The  
backing layer can be any appropriate thickness which will  
35       provide the desired protective and support functions. A  
suitable thickness will be from about 10 to about 200  
microns. Desirably, the thickness will be from about 15 to  
40       about 150 microns, and preferably be from about 20 to about  
100 microns.

45           In illustration of the dosage units provided by this  
invention, the FIG. 1 dosage unit is provided. The backing  
layer is selected from the above illustrative backing layer  
50       pharmaceutical-impermeable laminates. It has been found  
suitable to use as backing layer consisting of a laminate of  
aluminum foil and polyester film which is heat sealable,  
55       such as sold by 3M as Scotch Pak 1009. A non-porous mem-  
brane such as a non-porous (ethylene/vinyl acetate) copoly-

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mer film, which is bioacceptable, can be used as the permeability-regulating membrane. The non-porous (ethylene/vinyl acetate) copolymer film can be precast on a siliconized paper or other substrates to provide a receptacle of suitable dimensions to form the walls of the reservoir. To this reservoir receptacle is added the desired form of one or more pharmaceuticals. The pharmaceuticals can be dissolved in a solution for the pharmaceuticals and added in a suitable amount to the reservoir receptacle. Then, a sheet of the backing layer is selected. It is placed over the reservoir receptacle and heat sealed thereto. It has been found that a sealing temperature of about 350-400°F, such as 370°F, can ordinarily be used and a sealing pressure of 50 psi is suitable. The sealing conditions can be varied widely depending upon the thermal characters of the backing layer and permeability-regulating membrane used. The backing layer can extend around the sides of the reservoir receptacle. On a siliconized release liner using a pattern to form a peripheral adhesive ring, a peripheral ring of adhesive polymer is formed. This adhesive polymer ring mounted on the siliconized release liner is mounted and sealed to the outwardly extending portion of the backing layer.

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The adhesive polymer used in forming the ring can have a pharmaceutical microdispersed therein, for example, by dissolving the pharmaceutical in a biocompatible solution

5 and then stirring at a sufficiently high intensity to cause  
the pharmaceutical to be microdispersed in the adhesive  
10 polymer to form microreservoirs.

The one or more pharmaceuticals present in the reser-  
voirs can be selected from a wide variety. If desired, a  
15 gelling agent can be added to the macroreservoir solution to  
provide the macroreservoir in a semi-solid state. Also, the  
20 macroreservoir solution can be also microdispersed within an  
adhesive polymer as described above in connection with for-  
mation of the peripheral ring of the FIG. 1 dosage unit.  
25 This results in the pharmaceutical component of the reser-  
voir to be provided as microreservoirs of the pharmaceuti-  
30 cal.

The dosage units provided thereby can be stored appro-  
priately until it is desired to treat a subject with the  
35 dosage unit whereupon after removal of the peelable release  
liner, it is applied to the skin of the subject.

40 FIG. 1-(A) shows the top view of the dosage unit of  
FIG. 1.

45 FIG. 2 is substantially the same dosage unit design as  
provided by FIG. 1 with the exception that the pharmaceuti-  
cal A is contained in the macroreservoir compartment (drug-  
50 reservoir compartment A) and pharmaceutical B is present in  
microreservoir form in the peripheral adhesive ring (drug-  
reservoir compartment B). Provided is FIG. 2(A) showing the  
55 top view of the dosage unit of FIG. 2.

5           The permeability-regulating polymer membrane as  
employed in the dosage units shown in FIG. 1 and FIG. 2 can  
10 be selected from a number of polymeric membranes depending  
upon the rate of delivery desired and the pharmaceuticals  
administered by the dosage unit.

15           The permeability-regulating polymer membranes used are  
"non-porous", meaning essentially free of pores. The per-  
20 meability-regulating polymer membrane permits the pharma-  
ceutical to pass through the membrane along with any skin  
permeation-enhancing agent used. It has been found that a  
25 suitable non-porous polymer film for use in making the per-  
meability-regulating membrane for dosage units having a  
30 number of pharmaceutical components is a (ethylene/vinyl  
acetate) copolymer film. The vinyl acetate content of the  
film is suitably from about 4.5 to about 50 percent by mean  
35 weight of the copolymer, presently preferred for many uses  
the content is in the range of about 18 to about 40 percent  
40 by mean weight. The thickness of the film can also vary.  
Generally speaking, the thicker the film used, the slower  
45 the rate of transdermal absorption of the pharmaceutical  
component present in the reservoir. It has been found that  
ordinarily a membrane can be selected from those having a  
50 thickness of about 10 to about 100 microns. Ordinarily, a  
membrane having a thickness of about 20 to about 80 microns  
permits desired transdermal absorption and adequate  
55 strength. Other polymeric films can also be used so long as  
they are non-porous, bioacceptable, permit the pharmaceuti-

5 cal component to be transdermally absorbed at a desired rate  
10 and have adequate dimensional strength.

15 The reservoir medium employed to dissolve the pharmaceutical component in either a macroreservoir or microreservoirs can vary widely. It is desired that the reservoir medium can be prepared from a combination of two miscible  
20 co-solvents. It has been found that certain combinations of ethanol and water work well to provide high rates of transdermal absorption, which are constant, and give variability  
25 in the absorption rates. For example, if the pharmaceutical component has one or two hormonal steroids, for example, estradiol and a progestin, such as levonorgestrel, certain  
30 combinations of ethanol and water can be used as the reservoir medium to provide desirable constant rates of transdermal absorption over a period of 24 hours or longer and  
35 variability in the rates of absorption. It has been found that the combination of ethanol and water having about 55 to  
40 85 percent ethanol content, preferably about 60 to about 80 percent, and more preferably about 70 percent ethanol provide maximal rate of transdermal absorption. Combinations  
45 of other solvents can also be used so long as they provide the desired results.

50 It has also been found desirable to use a C<sub>3</sub>-C<sub>4</sub> alkane diol as the reservoir solvent. Preferred diol compounds  
55 useful in the compositions of the present invention include 1,2-propanediol, 1,3-propanediol, 1,2-butanediol, 1,3-

5 butanediol, 1,4-butanediol, or mixtures of these diol compounds. In compositions of the present invention, 1,2-propanediol and 1,2-butanediol are more preferred diol compounds; 1,2-propanediol is an especially preferred diol compound.

15 If one of the C<sub>3</sub>-C<sub>4</sub> alkane diols is selected for use as a reservoir solvent, the amount used will vary depending upon the pharmaceutical component and other agents present. Ordinarily, an amount of at least about 20 percent by weight of the solvent is used. Preferably, in making many dosage units, an amount of about 30 to about 90 percent is suitable, if, for example, 1,2-propanediol is used.

30 It is also desirable to use in combination with the miscible co-solvents by incorporating other agents, such as transdermal absorption-enhancing agents. It has been found suitable to use in combination with the combination of ethanol and water, an amount of a long chain alkanoic acid, such as oleic acid, or long-chain alcohol having, for example, decyl or lauryl alcohol. It has been also found useful to have present an effective amount of a lower alkyl ester of lactic acid such as ethyl lactate. Also, it has been found useful to have present an amount of agents sold under the designation Ceraphil, for example, Ceraphil 31 which has lauryl and myristyl lactate ester and lauryl and myristyl alcohol components.

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A suitable reservoir solution has been found to have the following weight ratio: Ceraphil 31, n-decyl alcohol, ethyl lactate and propylene alcohol, 1:1:1:2.

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If two pharmaceuticals are present in a reservoir, either of the macroreservoir or microreservoir type, at least one of the pharmaceuticals should be present in less than saturated amount in order that the absorption rate ratios of the two pharmaceuticals can be varied and also be maintained at a constant rate ratio.

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Aqueous gels of organic polymers which are bioacceptable and compatible with other components of a pharmaceutical-containing reservoir can be used to convert the reservoir medium to a semi-solid state. For example, a small amount of such aqueous gels as gelatin, agar, pectin, methyl cellulose and polyethylene glycols, hydroxypropyl cellulose, and polyvinyl pyrrolidone can be used. Ordinarily, a small amount of aqueous gels is adequate to provide the desired increase in viscosity or semi-solid state, for example, 1 to 4 percent in the use of pectin or agar.

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If it is desired that the pharmaceutical in a reservoir is present as microreservoirs, the microreservoirs can be formed by dissolving the pharmaceutical component in a desired reservoir medium, which is not a solvent for the polymeric material desired to be used in making the microreservoirs. A number of polymers are suitable, for example, a number of adhesive polymers can be used, for example, a

5           number of polyacrylate-based adhesive polymers, silicone  
elastomers, polyisobutylene, and the like.

10           The polymeric material selected must permit the pharma-  
ceutical to be released for the desired transdermal absorp-  
15           tion and not substantially affect the pharmaceutical compo-  
nent or the permeability-regulating membrane or other compo-  
nents. The reservoir medium containing dissolved/dispersed  
20           pharmaceutical and the polymeric material are combined in a  
suitable amount and agitated using suitable stirring or dis-  
persing means to cause microreservoirs to be formed and  
25           homogeneously dispersed in the polymeric material. It is  
normally desired that the microreservoirs be of a micronic  
30           diameter, such as 2 to about 200 microns, usually preferably  
about 5 to about 100 microns in diameter.

35           The adhesive polymers used in forming the adhesive  
element can be selected from known adhesives which are bio-  
acceptable and pressure-sensitive. It is suitable that the  
40           adhesive element be in the form of a ring peripheral to a  
central reservoir, if that is the type of dosage unit of the  
invention used. Known polyacrylate, polyisobutylene, sili-  
45           cone or the like adhesive polymers can be used. If a peri-  
pheral ring is made of such adhesive polymer, it can contain  
a pharmaceutical which is different from the pharmaceutical  
50           component of the central reservoir. The pharmaceutical from  
the peripheral ring can be present as microreservoirs or can  
55           be present in matrix polymer form wherein the pharmaceutical  
is microdispersed in the adhesive polymer.

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The dosage units can vary in surface area as desired. Generally, they do not exceed about 100 sq cm in area, suitably about 5 to about 80 sq cm, preferably about 10 to about 40 sq cm, generally about 5 to about 50 sq cm being a more preferable size. The dosage units can vary in shape as desired, such as circular, square, rectangular or other desired shape.

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The dosage units can be, as stated above, multi-regional wherein at least one pharmaceutical is present in one or more regions. The pharmaceuticals in such multi-regional dosage units of this invention are transdermally absorbed therefrom. The multi-regions can be in a form of a central core, with one or more concentric circular bands surrounding the core, in a form of adjacent rectangular regions, or other suitable arrangements of the multi-regions.

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The multi-regions can have the same or different pharmaceuticals to provide transdermal absorption thereof. The multi-regions can be in the form wherein the pharmaceutical is present in a macroreservoir covered with only a permeability-regulating polymer membrane, in a form wherein the pharmaceutical is in the form of microreservoirs wherein the region is covered or not covered with a permeability-regulating membrane, or one or more of the regions are in the form of a pharmaceutical-dispersing polymer matrix disc. It is preferred that at least one region of a multi-regional

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5 dosage unit of this invention be a macroreservoir covered  
with a permeability-regulating polymer membrane and provide  
10 a constant rate for at least 24 hours and the rate can be  
varied as desired.

15 A wide range of pharmaceuticals can be administered by  
the dosage units of this invention, so long as they are  
capable of being administered transdermally. It has been  
20 found that the dosage units are especially useful in admin-  
istering two pharmaceuticals from a reservoir covered with a  
permeability-regulating membrane wherein at least one phar-  
25 maceutical is contained in a reservoir medium in less than a  
saturated condition. Thereby, the pharmaceutical can be  
30 provided in a constant rate ratio for an extended number of  
hours, for example, at least a 24-hour period. Such dosage  
unit of this invention is especially useful in providing a  
35 combination of estrogenic and progestational steroids for  
either fertility regulation or estrogen replacement therapy.  
40 The reservoir medium can be modified to provide a variable  
rate of one or both of the steroids (or other pharmaceuti-  
cals) and the corresponding absorption rate ratios.

45 With regard to estrogenic steroids, 17-beta-estradiol  
is a natural and a preferred estrogen. Derivatives of 17-  
50 beta-estradiol which are biocompatible, capable of being  
absorbed transdermally and preferably bioconvertible to 17-  
55 beta-estradiol can also be used, if the amount of absorption  
meets the required daily dose of the estrogen component and  
if the steroid components are compatible. Such derivatives

5 of estradiol can be selected from esters, either mono- or  
10 di-esters. The monoesters can be either 3- or 17-esters.  
The estradiol esters can be, illustratively speaking, estra-  
diol-3,17-diacetate; estradiol-3-acetate; estradiol-17-ace-  
15 tate; estradiol-3,17-divalerate; estradiol-3-valerate;  
estradiol-17-valerate; 3-mono, 17 mono- and 3,17-dipivilate  
20 esters; 3-mono, 17-mono and 3,17-dipropionate esters; cor-  
responding cypionate, heptanoate, benzoate and the like  
esters; ethinyl estradiol; estrone; estriol; and other  
25 estrogenic steroids and derivatives thereof which are trans-  
dermally absorbable, including benzzestrol, chlorotrianisene,  
dienestrol, mestranol, and the like.

30 The progestational steroids can be selected from  
norethindrone, norgestimate, levonorgestrel (or norgestrel  
35 containing both levonorgestrel and its (+) enantiomer),  
norethynodrel, dydrogesterone, ethynodiol diacetate, deso-  
gestrel, 3-keto-desogestrel, hydroxyprogesterone caproate,  
40 medroxyprogesterone acetate, norethindrone, norethindrone  
acetate, norgestrel, progesterone, and the like.

45 Steroids which are androgenic can also be used in  
making the dosage units of this invention such as testos-  
terone and its esters, such as testosterone enanthate, 17-  
50 alpha-methyl testosterone, 19-nortestosterone and its  
esters, such as nandrolone decanoate and the like.

5 Transdermal delivery of testosterone and/or 17-alpha-methyl testosterone could be used in the treatment of hypo-  
10 gonadism or used as male contraceptive. When delivered in combination with an estrogen, such as 17-beta-estradiol, from the biregional patch, it could minimize the side  
15 effects of delivering androgen alone. These side effects include: muscular overdevelopment, weight gain, acne and increase in libido.  
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Transdermal delivery of medroxy progesterone acetate (MPA) can be used in the treatment of secondary amenorrhea  
25 and abnormal uterine bleeding due to hormonal imbalance. When delivered in combination with an estrogen, such as 17-beta-estradiol, from the biregional patch, it could minimize  
30 the side effects encountered by taking oral MPA (Provera, by Upjohn). These side effects include breakthrough bleeding, spotting, edema, change in menstrual flow, change in weight,  
35 acne, rash and insomnia, etc.

40 The ratios and the amounts of the estrogens and progestins to be administered on a daily basis are known to those skilled in the art. Reference is made, for example, to U.S.  
45 Patent No. 5,023,084.

Other pharmaceuticals, either alone or in combination,  
50 can be selected for use in carrying out this invention and can be selected from the following: alpha-[1(methylamino)-ethyl]-benzene methanol, which is useful as an adrenergic  
55 (bronchodilator); buprenorphine, N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl] propanamide, useful as a narcotic

5 analgesic; furosemide and 6-chloro-3, 4-dihydro-2H-1,2,4-  
10 benzothiadiazine-7-sulfonamide 1,1-dioxide, useful as diure-  
tics; and 2-diphenylmethoxy-N, N-dimethylethanamine, useful  
as an antihistamine. Other useful drugs include: anti-HIV  
15 drugs, such as dideoxy nucleoside; antimicrobial agents,  
such as penicillins, cephalosporins, tetracycline, oxytetra-  
cycline, chlortetracycline, chloramphenicol and sulfona-  
20 mides; sedatives and hypnotics, such as pentobarbital,  
sodium pentobarbital, secobarbital sodium, codeine, (a-  
25 bromoisovaleryl) urea, and carbromal; psychic energizers,  
such as 3-(2-aminopropyl) indole acetate and 3-(2-aminobutyl  
indole acetate; tranquilizers, such as diazepam, chlordiaze-  
30 poxide hydrochloride, reserpine, chlorpromazine hydro-  
chloride, and thiopropazate hydrochloride; hormones, such as  
35 adrenocorticosteroids, for example, 6-methyl-prednisolone;  
androgenic steroids, for example, testosterone, methyltes-  
tosterone, and fluoxymesterone; estrogenic steroids, for  
40 example, estrone, estradiol and ethinyl estradiol; progesta-  
tional steroids, for example, levonorgestrel, progesteron,  
45 17a-hydroxyprogesterone and acetate, medroxyprogesterone and  
acetate, 19-norprogesterone, and norethindrone; thyroxine;  
antipyretics, such as aspirin, salicylamide, methylsali-  
50 cylate, triethanolamine salicylate; morphine and other nar-  
cotic analgesics; hypoglycemic agents, for example, sulfonyl  
55 ureas such as glypizide, glyburide and chlorpropamide and  
insulin; antispasmodics, such as atropine, methscopolamine

5 bromide, methscopolamine bromide with phenobarbital, anti-  
malarials, such as the 4-aminoquinolines, 9-aminoquinolines,  
10 and pyrimethamine; adrenergic block agents, such as meto-  
prolo; antiarthritic agents, such as sulindac; nonsteroidal  
15 anti-inflammatory agents, such as ibuprofen and naproxen;  
vasodilators, such as dipyridamole, isosorbide dinitrate;  
antihypertension agents, such as propranolol, methyldopa and  
20 prazosin; contraceptive agents, such as levo-  
norgestrel/estradiol combination and norethindrone acetate  
combination; agents for treating duodenal ulcers, such as  
25 cimetidine; and nutritional agents, such as vitamins, essen-  
tial amino acids, and essential fats. The above listing of  
30 pharmaceuticals is merely exemplary of the transdermally  
applicable pharmaceuticals. It is contemplated that any  
35 pharmaceutical can be utilized may be transdermally adminis-  
tered by use of this invention.

The presence of enhancing agents in the dosage units  
40 together with the pharmaceutical is often highly useful. It  
has been found that the presence of oleic acid as an  
enhancing agent in certain dosage units of this invention is  
45 highly advantageous. Other enhancing agents which are use-  
ful in this invention can be selected from the following:  
50 long-chain alkanols, long-chain alkanolic acids and their  
esters, ceramide, dialkyl sulfoxide, surfactants, and the  
55 like.

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Example 1

10 A dosage unit as shown in FIG. 1 is fabricated. The  
backing layer employed is the following. The permeability-  
15 regulating polymer membrane used is EVA, 28 percent vinyl  
acetate, sold by 3M Co., 50 micron thick. The skin permea-  
tion rate of levonorgestrel is controlled by using the com-  
20 bination of ethanol and water with varying concentration or  
ratio as the dissolving solvent for levonorgestrel to form  
solution which is placed within the reservoir as shown in  
25 FIG. 1 as drug reservoir compartment. As shown in FIG. 3,  
the cumulative levonorgestrel amount of permeation ( $\text{mcg}/\text{cm}^2$   
 $\pm$  SEM) is varied greatly by varying the ratio of  
30 ethanol:water. It is shown that very little permeation is  
realized when 100 percent water is utilized as well as very  
low permeation is achieved with 100 percent ethanol. It is  
35 noted from the graphs of FIGS. 3A and 3B that greatly  
enhanced rates of permeation are realized at a ratio of  
ethanol:water of 60:40 and a ratio of 80:20 and 70:30. It  
40 is noted that of the ratios shown, the highest cumulative  
levonorgestrel permeation rate is realized by utilizing the  
45 70:30 ratio. The data with respect to the difference in the  
skin permeation of levonorgestrel as a function of the etha-  
50 nol:water ratio are shown on the graph of FIG. 4 wherein the  
skin permeation rate of levonorgestrel in  $\text{mcg}/\text{cm}^2/\text{hr.} \pm$  S.D.  
55 vs. ethanol:water ratio on a volume/volume basis is shown.

The following table shows the dependence of the skin permeation rate of levonorgestrel and enhancement based on the ethanol:water ratio in the reservoir solution used which contains the levonorgestrel.

Dependence of the Skin Permeation Rate  
of Levonorgestrel and Enhancement on the  
Volume Fraction of Ethanol in Reservoir Solution

Reservoir Solution <sup>(1)</sup>	(%V/V)	Skin Permeation Rate <sup>(2)</sup>	Enhancement <sup>(3)</sup> Factor
<u>Ethanol</u>	<u>Water</u>	(mcg/cm <sup>2</sup> /hr $\pm$ S.D.)	
0	100	0.03 (0.01)	1.0
20	80	0.09 (0.03)	3.0
40	60	0.47 (0.02)	15.7
60	40	2.40 (0.68)	80.0
70	30	7.69 (0.94)	256.3
80	20	4.01 (0.33)	133.7
100	0	1.33 (0.55)	44.3

(1) Saturated levonorgestrel solution

(2) Dorsal skin (n = 3 each) freshly excised from hairless rat.

(3) Compared to the skin permeation rate of levonorgestrel from reservoir solution having 100% (V/V) of water as the vehicle.

FIG. 5 shows the difference in the levonorgestrel permeation rate depending upon the content of vinyl acetate in the permeability-regulating polymer membrane as shown in FIG. 1 as permeability-regulating polymer membrane. It is shown that as the weight fraction of vinyl acetate in the

5 permeability-controlling membrane increases from 9 percent  
10 to 40 percent, the levonorgestrel permeation rate increases.

15 The particular permeability-regulating membrane utilized in this experiment is an (ethylene/vinyl acetate) copolymer as shown in FIG. 6. The rates of transdermal permeation (in  $\text{mcg}/\text{cm}^2/\text{hr} \pm \text{S.D.}$ ) of levonorgestrel in the  
20 hairless rat skin test utilizing a 50 micron (ethylene/vinyl acetate) copolymer membrane having variation in the weight fractions of vinyl acetate from 9% to 40% from a saturated  
25 levonorgestrel donor solution containing the ratio of ethanol:water of 70:30.

30 FIG. 7 shows the difference in cumulative levonorgestrel permeation vs. thickness of the permeability-regulating (ethylene/vinyl acetate) copolymer membrane shown in FIG. 1, along with a comparison with the rate of permeation wherein  
35 no membrane is utilized, i.e., skin alone. A saturated levonorgestrel solution of ethanol:water of 70:30 on a V/V basis. Two percent of oleic acid was utilized. The membrane polymer contained 28% vinyl acetate. It is noted that  
40 differences in the thickness of membrane varied from 30 microns to 50 microns and 100 microns. It is noted that substantially more levonorgestrel was absorbed transdermally  
45 when a 30 micron membrane was utilized and that the lowest level of permeation was observed when the 100 micron membrane was used.  
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5           FIG. 8 shows the relationship of the permeation rate of  
levonorgestrel across the permeability-regulating polymer  
10 membrane utilizing a (ethylene/vinyl acetate) membrane con-  
taining 28 percent vinyl acetate and the reservoir solution  
15 containing 70% ethanol and 2% oleic acid and the remainder  
being water. It shows that a higher rate of permeation is  
obtained utilizing the 30 micron thickness and that a higher  
20 rate was obtained using a 50 micron thickness than was  
obtained with the 100 micron thickness.

25           FIG. 9 shows the rate of skin permeation of levonorges-  
trel (in mcg/cm<sup>2</sup>/hr  $\pm$  S.D.) from a reservoir solution having  
varying ratios of ethanol:water on a V/V basis. Reservoir  
30 solution contains 5 percent of either azone or 5 percent  
oleic acid as an enhancer as compared to a reservoir solu-  
tion containing neither of the enhancing agents. In each  
35 case it is shown that the best skin permeation rate is  
obtained in the range of 60 to 80 percent ethanol. When  
40 utilizing 100 percent ethanol with no enhancing agent, about  
2 mcg of levonorgestrel has been administered per hour per  
45 cm<sup>2</sup>.

50           FIG. 10 shows the change in permeation rate (on a  
mcg/cm<sup>2</sup>/hr basis) from a saturated levonorgestrel reservoir  
solution having a ratio of ethanol:water of 70:30 utilizing  
a permeability-regulating membrane as shown in FIG. 1 where-  
55 in the vinylacetate content is 28% and the thickness is 50  
microns. The rate of transdermal absorption is shown vs.  
the concentration of oleic acid as the enhancing agent.

FIG. 11 shows the effect of estradiol loading dose on the permeation rates of levonorgestrel and estradiol across a permeability-regulating (ethylene/vinyl acetate) membrane wherein the vinyl acetate content is 28% and the thickness thereof is 50 microns. Utilized in this evaluation was the hairless rat skin test as described above. The reservoir solution was a saturated levonorgestrel solution wherein the ethanol concentration is 70% and the concentration of oleic acid as the enhancing agent is 2%. Permeation rates (on the basis of  $\text{mcg}/\text{cm}^2/\text{hr}$ ) are shown for estradiol and levonorgestrel. In the graph, the loading dose of estradiol is varied from one to 15 milligrams/milliliter in the reservoir solution.

FIG. 12 is a curve showing the ratio of the cumulative transdermal absorption of levonorgestrel over the cumulative transdermal absorption of estradiol. The data in the graph show that as the loading dose of estradiol is increased, the permeation rate ratio of levonorgestrel over estradiol varies from greater than unity to less than unity. The permeation rate ratio of levonorgestrel over estradiol utilizing a 2 milligram/milliliter loading of estradiol is about 6.5 and at 5 milligram/milliliter loading of estradiol, the permeation rate ratio of levonorgestrel over estradiol is reduced to about 1 and is further reduced to about 0.2 at an estradiol loading of 15 milligrams/milliliter.

FIG. 13 shows the cumulative estradiol permeation (based on  $\text{mcg}/\text{cm}^2/\text{hr} \pm \text{S.D.}$ ) utilizing a dosage unit such as that shown in FIG. 1 utilizing human cadaver skin test procedure. The transdermal absorption of estradiol is from a reservoir solution saturated with levonorgestrel. Various estradiol concentrations are utilized in the comparative testing, varying from an estradiol loading which is a saturated solution to 10, 5, 2, 1 and 0.2 milligrams/milliliter of estradiol loading. Utilizing a dosage unit such as that shown in FIG. 1, cumulative levonorgestrel permeation (based on  $\text{mcg}/\text{cm}^2 \pm \text{S.D.}$ ) is shown. A permeation profile of levonorgestrel across a permeability-regulating membrane which is an (ethylene/vinyl acetate) membrane containing 28 percent vinyl acetate and utilizing human cadaver test procedure.

FIG. 14 shows a permeation profile of levonorgestrel across an (ethylene/vinyl acetate) membrane-covered human cadaver skin. Various estradiol loadings are used in the reservoir solution varying from 0.2 mg/ml to saturation.

FIG. 15 shows a dosage unit as shown in FIG. 1 wherein the reservoir solution has varying levels of estradiol loading and the permeation rates of levonorgestrel and estradiol have been varied depending upon estradiol loading. A permeability-regulating (ethylene/vinyl acetate) membrane is utilized as the permeation-controlling membrane shown in FIG. 1. The human cadaver skin test was utilized. The data show the change in the permeation rates (based upon

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mcg/cm<sup>2</sup>/hr  $\pm$  S.D.) of both estradiol and levonorgestrel from a reservoir solution consisting of saturated levonorgestrel with a ratio of ethanol:water at 70:28 by volume. The reservoir solution also contains 2% of oleic acid. The permeability-regulating membrane used comprises 28% vinyl acetate and has a thickness of 50 microns. The estradiol loading varies from zero to 15 milligrams/milliliter. It is shown that the permeation rate for levonorgestrel at zero percent estradiol loading in this system is about 1 and slightly declines to about 0.7 mcg/cm<sup>2</sup>/hr at 15 milligrams/milliliter of estradiol.

FIG. 16 shows a graph wherein the effect of estradiol loading on permeation rate ratio of levonorgestrel over estradiol. The graph shows that the permeation rate ratio is greatly reduced depending upon the loading dose of estradiol. The permeability-regulating (ethylene/vinyl acetate) membrane utilized has 28 percent vinyl acetate and has a thickness of 50 microns. The reservoir solution, which is saturated with levonorgestrel, has 70 percent ethanol and 2 percent oleic acid content. The human cadaver skin test is utilized.

FIG. 17 is a graph showing the effect of drug releasing area on dosage rate ratio of levonorgestrel over estradiol. A dosage unit of the type shown in FIG. 2 is utilized. The reservoir solution in drug-reservoir compartment A is a saturated levonorgestrel solution wherein the ethanol:water

5 has a ratio of 70:30 and the permeation rate of levonorges-  
trel is 21.84 mcg/cm<sup>2</sup>/day. The permeability-regulating  
10 membrane is an (ethylene/vinylacetate) membrane containing  
28 percent vinyl acetate and having a thickness of 50  
15 microns. The permeation rate of estradiol in the polyacry-  
late adhesive used to make the peripheral ring as shown as  
drug-reservoir compartment B in the FIG. 2 dosage unit is  
20 24.36 mcg/cm<sup>2</sup>/day. As the area of the pharmaceutical-  
releasing area pertaining to levonorgestrel is increased  
25 over the pharmaceutical-releasing area of estradiol, the  
ratio of daily dosage rate of levonorgestrel over the daily  
dosage rate of estradiol is increased. It is shown, for  
30 example, that the ratio of the daily dosage rate of levonor-  
gestrel/daily dosage rate of estradiol changes from about 2  
35 when the ratio of the pharmaceutical-releasing area of levo-  
norgestrel/pharmaceutical-releasing area of estradiol is 2  
to about a daily dosage rate of levonorgestrel/daily dosage  
40 rate of estradiol of about 7.5 when the permeability-  
releasing area of levonorgestrel/pharmaceutical-releasing  
45 area of estradiol is 8. The following table compares the  
skin permeation rates of estradiol and levonorgestrel across  
permeability-regulating membranes of different compositions  
50 when utilized in the human cadaver skin test.

Comparison Between Skin Permeation Rates of Estradiol  
and Levonorgestrel Across Various Polymeric Membranes  
Applied on Human Cadaver Skin<sup>(1)</sup>

<u>Membrane</u>	<u>Thickness</u> (micron)	<u>Permeation Rate<sup>(2)</sup></u> (mcg/cm <sup>2</sup> hr $\pm$ S.D.)	
		<u>Estradiol</u>	<u>Levonorgestrel</u>
(Ethylene/vinyl acetate) Copolymer <sup>(3)</sup>	51	0.17 (0.02)	0.64 (0.16)
Polyethylene <sup>(4)</sup>	51	0.93 (0.18)	3.01 (0.58)
Silicone	300	0.00	0.17 (0.02)

(1) Human cadaver skin (female, 34 years old; thigh region) covered with polymeric membrane.

(2) From a saturated solution of levonorgestrel, in 70% ethanol and 2% oleic acid, which contains 0.5 mg/ml of estradiol.

(3) 3M Co. (VAc, 28% W/W); 51 micron)

(4) 3M Co. (microporous, 18 micron; void volume, 78%)

#### Example 2

A bi-regional transdermal drug delivery system which can simultaneously deliver a progestin, such as levonorgestrel (LNG) and an estrogen, such as 17-beta-estradiol (E2) from its central and peripheral regions, respectively, is fabricated by using the following processes and equipment:

Thoroughly mix 0.52 part of E2, 10.81 parts of oleic acid (OA) and 88.67 parts of polyacrylate adhesive solution (Duro-Tak 80-1054, by National Starch and Chemical Co., New Jersey, which contains 36% of solid) by weight in a container to form a homogeneous E2/OA adhesive solution. This

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solution is coated onto a silicone-coated release liner (Akrosil B2M) by a specially-designed pattern coating device to form a circular ring of peripheral region. This peripheral region has an inner and outer radius of 1.59 cm and 2.18 cm, respectively, which gives a 0.59 cm width and 7 sq cm to the area of the region. The wet thickness of the coating of this adhesive solution is controlled at 500 microns which is then cured in an oven at 60°C for 10 minutes to form the dried matrix of peripheral region about 200 microns thickness. The peripheral region obtained by this fabrication process is thereafter named Intermediate Product A (IP-A).

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Oleic acid, ethanol and water are mixed thoroughly at the weight ratio of 1:37:14 to form a homogeneous hydro-alcoholic solution system (HASS). An amount of 0.0036 part by weight of LNG is dissolved in 1.000 part by weight of HASS to form a homogeneous LNG/HASS solution. An amount of 400 microliters of LNG/HASS solution is carefully applied by a dispenser onto a piece of 50 micron-thick heat-sealable (ethylene/vinyl acetate) membrane (EVA, 28% vinyl acetate, by 3M Co.) which was precast on the siliconized paper release liner. The dispensed LNG/HASS solution is quickly covered with a piece of drug-impermeable/heat-sealable backing film (Scotch Pak 1109 by 3M Co.). The central region of this biregional drug delivery system is then formed by thermally sealing the backing film to the EVA film by a spe-

5 cially-designed heat seal machine. Sealing process is per-  
formed at 370°F and 50 psi for 1 (one) second of dwell time.  
10 The central region (7 sq cm in size) obtained by this  
process is designated Intermediate Product B (IP-B).

15 To complete the fabrication of the biregional transder-  
mal drug delivery system, IP-A is carefully laminated on the  
IP-B by a laminating device. The final product (15 sq cm in  
20 size), which is in the form of a transdermal patch, can be  
cut out by a die cutter.

25 The novel design of this patch product will allow the  
two drugs to be delivered simultaneously from a single unit  
of transdermal patch. LNG is delivered from the central  
30 region, while E2 is delivered from the peripheral region.  
In addition to changing the formulation ingredients in each  
region, the daily delivery rate of each drug can be altered  
35 by changing the relative size of the surface area of the two  
regions. This final product has the equal size of surface  
40 area (7 cm. sq) for the central and peripheral regions to  
allow desired amount of LNG and E2, respectively, to be  
delivered. In the in-vitro skin permeation study, this  
45 final product is found to give permeation rate of 0.62 and  
0.30 mcg/sq cm/hr of LNG and E2, respectively, which can be  
50 translated into the daily delivery rate of 104.2 mcg of LNG  
and 50.4 mcg of E2.

5

## Example 3

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A bi-regional transdermal drug delivery system, which can simultaneously deliver a combined dosage of progestin, such as levonorgestrel (LNG), and estrogen, such as 17-beta-estradiol (E2), from its central region, is fabricated by using the following processes and equipment:

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Thoroughly mix 5.06 parts of Ceraphil 31 (by Van Dyk/New Jersey), 94.94 parts of polyacrylate adhesive solution (Duro-Tak 80-1054, by National Starch and Chemical Co./New Jersey, which contains 48% of solid) by weight in a container to form a homogeneous adhesive solution. This solution is coated onto a silicone-coated release liner (Akrosil B2M) by a specially-designed pattern coating device to form a circular ring of peripheral region. This peripheral region has an inner and outer radius of 1.59 cm and 2.18 cm, respectively, which gives 0.59 cm to the width and 7 sq cm to the area of the region. The wet thickness of the coating of this adhesive solution is controlled at 500 microns which is then cured in an oven at 60°C for 10 minutes to form the dried matrix of peripheral region about 220 microns thick. The peripheral region obtained by this process is designated Intermediate Product A (IP-A).

50

55

Oleic acid, ethanol and water are mixed thoroughly at the weight ratio of 1:37:14 to form a homogeneous hydro-alcoholic solvent system (HASS). An amount of 0.0010 part by weight of E2 and 0.0036 part by weight of LNG are dissolved in 1.000 part by weight of HASS to form a homogeneous

5 E2/LNG/HASS solution. An amount of 400 microliters of  
10 E2/LNG/HASS solution is carefully applied by a dispenser  
onto a piece of 50 micron-thick heat-sealable (ethylene/  
15 vinyl acetate) membrane (EVA, 28% vinyl acetate, by 3M Co.)  
which was precast on the siliconized paper release liner.  
The dispensed E2/LNG/HASS solution is quickly covered with a  
20 piece of drug-impermeable/heat-sealable backing film (Scotch  
Pak 1109 by 3M Co.). The central region of this biregional  
drug delivery system is then formed by thermally sealing the  
25 backing film to the EVA film by a specially-designed heat  
seal machine. The sealing process is performed at 370°F and  
30 50 psi for 1 (one) second of dwell time. The central region  
(7 sq cm in size) obtained by this process is designated  
Intermediate Product B (IP-B).

35 To complete the fabrication of the biregional transder-  
mal drug delivery system, IP-A is carefully laminated onto  
40 the IP-B by a laminating device. The final product (15 sq  
cm in size), which is in the form of a transdermal patch, is  
cut out by a die cutter.

45 The novel design of this patch product will allow the  
two drugs to be delivered simultaneously from a single  
50 transdermal patch. Both E2 and LNG are delivered from the  
central region of this biregional transdermal patch. The  
peripheral region, which is made up of a pressure sensitive  
55 adhesive that contains a water-repelling tackifier (Ceraphil  
31) composition: lauryl lactate 50-60 percent, myristyl

5 lactate 15-20 percent, lauryl alcohol 10-20 percent,  
myristyl alcohol 2-10 percent will ensure the central region  
10 to have good contact with skin. In addition to varying the  
thickness and/or the vinyl acetate content of the EVA mem-  
brane, the daily delivery rate of each drug can be altered  
15 by changing their concentration in the HASS that is sealed  
in the central region. This dosage unit has the equal size  
of surface area (7 sq cm) for the central and peripheral  
20 regions to allow desired doses of LNG and E2 to be  
delivered. In the in-vitro skin permeation study, this  
25 final product was found to give permeation rate of 0.62 and  
0.26 mcg/sq cm/hr of LNG and E2, respectively, which can be  
translated into the daily delivery rate of 104.2 mcg of LNG  
30 and 43.7 mcg of E2. Another dosage unit formulation in  
which the central region is made up of 0.005 part by weight  
35 of E2 and 0.001 part by weight of LNG in 1.000 part by  
weight of HASS, is found to give human cadavers kin permea-  
tion rate of 1.63 and 0.25 mcg/sq cm/hr, respectively, in an  
40 in vitro test. These skin permeation rates of E2 and LNG  
can be translated into daily delivery rate of 273.8 and 42.0  
45 mcg/day, respectively.

#### 50 Example 4

A bi-regional transdermal drug delivery system which  
55 can simultaneously deliver a progestin, such as levonorges-  
trel (LNG), and an estrogen, such as 17-beta-estradiol (E2),

5 from its central and peripheral region, respectively, is  
fabricated by using the following processes and equipment:

10 Thoroughly mix 0.48 part of E2, 9.68 parts of oleic  
acid (OA) and 89.84 parts of polyacrylate adhesive solution  
15 (Duro-Tak 80-1054, by National Starch and Chemical Co., New  
Jersey, which contains 36% of solid) by weight in a contain-  
er to form a homogeneous E2/OA adhesive solution. This  
20 solution is coated onto a silicone-coated release liner  
(Akrosil B2M) by a specially-designed pattern coating device  
to form a circular ring of peripheral region. This peri-  
25 pheral region has an inner and outer radius of 0.9 cm and  
1.78 cm, respectively, which provides a 0.88 cm width and  
30 7.46 sq cm area of the region. The wet thickness of the  
coating of this adhesive solution is controlled at 500  
35 microns which is then cured in an oven at 60°C for 10  
minutes to form the dried matrix of peripheral region of  
about 200 microns thick. The peripheral region obtained by  
40 this product is designated Intermediate Product A (IP-A).

45 Ceraphil 31 (by Van Dyk/New Jersey), n-decyl alcohol,  
dimethyl sulfoxide and ethanol are mixed thoroughly at the  
weight ratio of 1:1:1:2 to form a homogeneous alcoholic  
enhancer system (AES). Dissolve excess of LNG in AES to  
50 form an oversaturated LNG/AES solution. Carefully dispense  
130 microliter of LNG/AES solution by a dispenser onto a  
piece of 50 micron-thick heat-sealable (ethylene/vinyl ace-  
55 tate) membrane (EVA, 28% vinyl acetate, by 3M Co.) which was  
precast on the siliconized paper release liner. The dis-

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pensed LNG/AES solution is quickly covered with a piece of drug-impermeable/heat-sealable backing film (Scotch Pak 1109 by 3M Co.). The central region of this biregional drug delivery system is then formed by thermally sealing the backing film to the EVA film by a specially-designed heat seal machine. The sealing process is performed at 370°F and 50 psi for 1 (one) second of dwell time. The central region (2.01 sq cm in size) obtained by this process is designated Intermediate Product B (IP-B).

To complete the fabrication of the biregional transdermal drug delivery system, IP-A is carefully laminated on the IP-B by a specially-designed laminating device. The final dosage unit (10 sq cm in size) is cut out by a die cutter.

The novel design of this patch product will allow the two drugs to be delivered simultaneously from a single transdermal dosage unit. LNG is delivered from the central region, while E2 is delivered from the peripheral region. In addition to variation of the formulation ingredients in each region, the daily delivery rate of each drug can be altered by varying the relative size of the surface area of the two regions. This final product has the 2.01 and 7.46 sq cm of surface area for the central and peripheral regions, respectively, to allow desired amount of LNG and E2, respectively, to be delivered. In the in-vitro skin permeation study, this final dosage unit is found to give permeation rates of 3.18 and 0.28 mcg/sq cm/hr of LNG and

5 E2, respectively, which can be translated into the daily  
10 delivery rate of 153.3 mcg of LNG and 50.1 mcg of E2.

10 Example 5

15 A bi-regional transdermal drug delivery system which  
can simultaneously deliver a progestin, such as levonorges-  
20 tret (LNG), and an estrogen, such as 17-beta-estradiol (E2),  
from its central and peripheral region, respectively, is  
fabricated by using the following processes and equipment:

25 Thoroughly mix 0.48 part of E2, 9.68 parts of oleic  
acid (OA) and 89.64 parts of polyacrylate adhesive solution  
(Duro-Tak 80-1054, by National Starch and Chemical Co., New  
30 Jersey, which contains 36% of solid) by their weight in a  
container to form a homogeneous E2/OA adhesive solution.  
35 This solution is coated onto a silicone-coated release liner  
(Akrosil B2M) by a specially-designed pattern coating device  
to form a circular ring of peripheral region. This peri-  
40 pheral region has an inner and outer radius of 0.9 cm and  
1.78 cm, respectively, which gives a region having a 0.88 cm  
45 width and a 7.46 sq cm area. The wet thickness of the coat-  
ing of this adhesive solution is controlled at 500 microns  
which is then cured in an oven at 60°C for 10 minutes to  
50 form the dried matrix of peripheral region about 200 microns  
thick. The peripheral region obtained by this product is  
55 designated Intermediate Product A (IP-A).

5 Ceraphil 31 (by Van Dyk/New Jersey), n-decyl alcohol,  
ethyl lactate and propylene glycol are mixed thoroughly at  
10 the weight ratio of 1:1:1:2 to form a homogeneous nonethano-  
lic enhancer solvent system (NES). Dissolve excess of LNG  
15 in NES to form an oversaturated LNG/NES solution. Carefully  
dispense 150 microliter of LNG/NES solution by a dispenser  
onto a piece of 50 micron-thick heat-sealable (ethylene/  
20 vinyl acetate) membrane (EVA, 28% vinyl acetate, by 3M Co.)  
which was precast on the siliconized paper release liner.  
Quickly cover the dispensed LNG/NES solution with a piece of  
25 drug-impermeable/heat-sealable backing film (Scotch Pak 1109  
by 3M Co.). The central region of this biregional drug  
30 delivery system is then formed by thermally sealing the  
backing film to the EVA film by a specially-designed heat  
seal machine. Sealing process was performed at 370°F and 50  
35 psi for 1 (one) second of dwell time. The central region  
(2.01 sq cm in size) obtained by this process is designated  
40 Intermediate Product B (IP-B).

To complete the fabrication of the biregional transder-  
mal drug delivery system, IP-A is carefully laminated on the  
45 IP-B by a laminating device. The final dosage unit (10 sq  
cm in size), is cut out by a die cutter.

50 The novel design of this patch product allows the two  
drugs to be delivered simultaneously from a single transder-  
mal dosage unit. LNG is delivered from the central region,  
55 while E2 is delivered from the peripheral region. In addi-  
tion to variation of the formulation ingredients in each

5 region, the daily delivery rate of each drug can be altered  
10 by changing the relative size of the surface area of the two  
regions. This final dosage unit product has the 2.01 and  
15 7.46 sq cm of surface area for the central and peripheral  
regions, respectively, to allow desired amount of LNG and  
E2, respectively, to be delivered. In the in-vitro skin  
20 permeation study, this final dosage unit is found to give  
permeation rate of 2.32 and 0.28 mcg/sq cm/hr of LNG and E2,  
respectively, which can be translated into the daily  
25 delivery rate of 112.0 mcg of LNG and 50.1 mcg of E2.

#### 30 Example 6

A bi-regional transdermal drug delivery system which  
can simultaneously deliver a progestin, such as norethin-  
35 drone (NET), and an estrogen, such as ethinyl estradiol  
(EE), from its central and peripheral regions, respectively,  
can be fabricated by using the following processes and  
40 equipment:

Thoroughly mix 0.65 part of EE, 8.96 parts of n-decyl  
45 alcohol (n-DA) and 90.39 parts of polyacrylate adhesive  
solution (Duro-Tak 80-1054, by National Starch and Chemical  
Co., New Jersey, which contains 36% of solid) by weight in a  
50 container to form a homogeneous EE/n-DA adhesive solution.  
This solution is coated onto a silicone-coated release liner  
55 (Akrosil B2M) by a specially-designed pattern coating device  
to form a circular ring of peripheral region. This peri-

5 pheral region has an inner and outer radia of 1.956 cm and  
2.52 cm, respectively, which gives 0.66 cm to the width and  
10 7.93 sq cm to the area of the region. The wet thickness of  
the coating of this adhesive solution is controlled at 500  
15 microns which is then cured in an oven at 60°C for 10  
minutes to form the dried matrix of peripheral region about  
200 microns thick. The peripheral region obtained by this  
20 product is designated Intermediate Product A (IP-A).

Ceraphil 31 (by Van Dyk/New Jersey), n-decyl alcohol,  
25 ethyl lactate and propylene glycol are mixed thoroughly at  
the weight ratio of 1:1:1:2 to form a homogeneous nonethano-  
lic enhancer system (NES). Dissolve excess of LNG in NES to  
30 form an oversaturated NET/NES solution. Carefully apply 150  
microliter of NET/NES solution by a dispenser onto a piece  
of 50 micron-thick heat-sealable (ethylene/vinyl acetate)  
35 membrane (EVA, 28% vinyl acetate, by 3M Co.), which was  
precast on a siliconized paper release liner. Quickly cover  
40 the dispensed NET/NES solution with a piece of drug-imper-  
meable/heat-sealable backing film (Scotch Pak 1109 by 3M  
Co.). The central region of this biregional drug delivery  
45 system is then formed by thermally sealing the backing film  
to the EVA film by a specially-designed heat seal machine.  
50 Sealing process was performed at 370°F and 50 psi for 1  
(one) second of dwell time. The central region (12.0 sq cm  
in size) obtained by this process is designated Intermediate  
55 Product B (IP-B).

5 To complete the fabrication of the biregional transder-  
mal drug delivery system, IP-A is carefully laminated onto  
10 the IP-B by a laminating device. The final product (20 sq  
cm in size), which is in the form of a transdermal patch, is  
cut out by a die cutter.

15 The novel design of this patch product will allow the  
two drugs to be delivered simultaneously from a single  
20 dosage unit. NET is delivered from the central region which  
does not contain ethanol as solvent, while EE is delivered  
from the peripheral region. In addition to changing the  
25 formulation ingredients in each region, the daily delivery  
rate of each drug can be altered by varying the relative  
30 size of the surface area of the two regions. This final  
product has 12.0 and 7.93 sq cm of surface area for the  
central and peripheral regions, respectively, to allow  
35 desired amount of NET and EE, respectively, to be delivered.  
In the in-vitro skin permeation study, this final product  
40 was found to give permeation rate of 2.69 and 0.19 mcg/sq  
cm/hr of NET and EE, respectively, which can be translated  
into the daily delivery rate of 774.7 mcg of NET and 36.2  
45 mcg of EE.

#### 50 Example 7

55 A bi-regional transdermal drug delivery system which  
can simultaneously deliver a progestin, such as medroxy  
progesterone acetate (MPA), and an estrogen, such as 17-  
beta-estradiol (E2), from its central and peripheral region,

5  
respectively, can be fabricated by using the following  
processes and equipment:

10  
Thoroughly mix 0.48 part of E2, 9.68 parts of isopropyl  
myristate (IPM) and 89.84 parts of polyacrylate adhesive  
15  
solution (Duro-Tak 80-1054, by National Starch and Chemical  
Co., New Jersey, which contains 36% of solid) by their  
weight in a container to form a homogeneous E2/IPM adhesive  
20  
solution. This polyacrylate adhesive has about 5 percent  
vinyl acetate polymer unit content. This solution is coated  
25  
onto a silicone-coated release liner (Akrosil B2M) by a  
specially-designed pattern coating device to form a circular  
ring of peripheral region. This peripheral region has an  
30  
inner and outer radia of 2.36 cm and 2.82 cm, respectively,  
which gives 0.46 cm to the width and 7.50 sq cm to the area  
35  
of the region. The wet thickness of the coating of this  
adhesive solution is controlled at 500 microns which is then  
cured in an oven at 60°C for 10 minutes to form the dried  
40  
matrix of peripheral region about 200 microns thick. The  
peripheral region obtained by this product is designated  
45  
Intermediate Product A (IP-A).

Ceraphil 31 (by Van Dyk/New Jersey), n-decyl alcohol,  
ethyl lactate and ethanol are mixed thoroughly at the weight  
50  
ratio of 1:1:1:2 to form a homogeneous alcoholic enhancer  
system (AES). Dissolve excess of MPA in AES to form an  
55  
oversaturated MPA/AES solution. Carefully dispense 150  
microliter of MPA/AES solution by a dispenser onto a piece

5 of 50 micron-thick heat-sealable (ethylene/vinyl acetate)  
membrane (EVA, 28% vinyl acetate, by 3M Co.) which was pre-  
10 cast on the siliconized paper release liner. Quickly cover  
the dispensed MPA/AES solution with a piece of drug-imper-  
15 meable/heat-sealable backing film (Scotch Pak 1109 by 3M  
Co.). The central region of this biregional drug delivery  
system is then formed by thermally sealing the backing film  
20 to the EVA film by a specially-designed heat seal machine.  
Sealing process was performed at 370°F and 50 psi for 1  
25 (one) second of dwell time. The central region (16.0 sq cm  
in size) obtained by this process is designated Intermediate  
Product B (IP-B).

30 To complete the fabrication of the biregional transder-  
mal drug delivery system, IP-A is carefully laminated onto  
the IP-B by a laminating device. The final product (25.0  
35 sq cm in size), which is in the form of a transdermal patch,  
can be cut out by a die cutter.

40 The novel design of this patch product will allow the  
two drugs to be delivered simultaneously from a single  
dosage unit. MPA is delivered from the central region,  
45 while E2 is delivered from the peripheral region. In addi-  
tion to variation of the formulation ingredients in each  
50 region, the daily delivery rate of each drug can be altered  
by changing the relative size of the surface area of the two  
regions. This final product has the 16.0 and 7.50 sq cm of  
55 surface area for the central and peripheral regions, respec-  
tively, to allow desired amount of MPA and E2, respectively,

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to be delivered. In the in-vitro skin permeation study, this final product was found to give permeation rate of 39.13 and 0.31 mcg/sq cm/hr of MPA and E2, respectively, which can be translated into the daily delivery rate of 15.03 mcg of MPA and 55.8 mcg of E2.

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#### Example 8

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30

A bi-regional transdermal drug delivery system which can simultaneously deliver two androgens, such as testosterone (T) and 17-alpha-methyl testosterone (m-T) and an estrogen, such as 17-beta-estradiol (E2), from its central and peripheral region, respectively, is fabricated by using the following processes and equipment:

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Thoroughly mix 0.65 part of E2, 8.96 parts of n-decyl alcohol (n-DA) and 90.39 parts of polyacrylate adhesive solution (Duro-Tak 80-1054, by National Starch and Chemical Co., New Jersey, which contains 36% of solid) by their weight in a container to form a homogeneous E2/n-DA adhesive solution. This solution is coated onto a silicone-coated release liner (Akrosil B2M) by a specially-designed pattern coating device to form a circular ring of peripheral region. This peripheral region has an inner and outer radia of 1.96 cm and 2.52 cm, respectively, which gives 0.56 cm to the width and 7.93 sq cm to the area of the region. The wet thickness of the coating of this adhesive solution is controlled at 500 microns which is then cured in an oven at

5 60°C for 10 minutes to form the dried matrix of peripheral  
region about 200 microns thick. The peripheral region  
10 obtained by this product is designated Intermediate Product  
A (IP-A).

15 Ceraphil 31 (by Van Dyk/New Jersey), n-decyl alcohol,  
ethyl lactate and propylene glycol are mixed thoroughly at  
the weight ratio of 1:1:1:2 to form a homogeneous nonethano-  
20 lic enhancer system (NES). Dissolve excess amounts of T and  
m-T in NSS to form an oversaturated T and m-T/NES solution.  
Carefully dispense 150 microliter of T and m-T/NES solution  
25 by a dispenser onto a piece of 50 micron-thick heat-sealable  
(ethylene/vinyl acetate) membrane (EVA, 28% vinyl acetate,  
30 by 3M Co.) which was precast on the siliconized paper  
release liner. Quickly cover the dispensed T and m-T/NES  
35 solution with a piece of drug-impermeable/heat-sealable  
backing film (Scotch Pak 1109 by 3M Co.). The central  
region of this biregional drug delivery system is then  
40 formed by thermally sealing the backing film to the EVA film  
by a specially-designed heat seal machine. Sealing process  
45 was performed at 370°F and 50 psi for 1 (one) second of  
dwell time. The central region (12.0 sq cm in size)  
obtained by this process is designated Intermediate Product  
50 B (IP-B).

55 To complete the fabrication of the biregional transder-  
mal drug delivery system, IP-A is carefully laminated onto  
the IP-B by a laminating device. The final product (20 sq

5 cm in size), which is in the form of a transdermal patch, is cut out by a die cutter.

10 The novel design of this patch product will allow the two drugs to be delivered simultaneously from a single dosage unit of transdermal patch. T and m-T are delivered  
15 from the central region, while E2 is delivered from the peripheral region. In addition to changing the formulation ingredients in each region, the daily delivery rate of each drug can be altered by modifying the relative size of the  
20 surface area of the two regions. This final product has 12.0 and 7.93 sq cm of surface area for the central and peripheral regions, respectively, to allow desired amount of T, m-T and E2, respectively, to be delivered. In the in-  
25 vitro skin permeation study, this final dosage unit is found to give permeation rates of 14.34, 13.64 and 0.24 mcg/sq cm/hr of T, m-T and E2, respectively, which can be translated into the daily delivery rate of 4,130.0 mcg of T,  
30 3,928.3 mcg of m-T and 45.7 mcg of E2.

#### 45 Example 9

A bi-regional transdermal drug delivery system which can simultaneously deliver a progestin, such as progesterone  
50 (P4), and an estrogen, such as 17-beta-estradiol (E2), from its central and peripheral regions, respectively, can be fabricated by using the following processes and equipment:  
55

5           Thoroughly mix 0.48 part of E2, 9.68 parts of isopropyl  
myristate (IPM) and 89.84 parts of polyacrylate adhesive  
10       solution (Duro-Tak 80-1054, by National Starch and Chemical  
Co., New Jersey, which contains 36% of solid) by weight in a  
15       container to form a homogeneous E2/IPM adhesive solution.  
This solution is coated onto a silicone-coated release liner  
(Akrosil B2M) by a specially-designed pattern coating device  
20       to form a circular ring of peripheral region. This peri-  
pheral region has an inner and outer radii of 2.36 cm and  
2.82 cm, respectively, which gives a region having 0.46 cm  
25       width and 7.50 sq cm area. The wet thickness of the coating  
of this adhesive solution is controlled at 500 microns which  
30       is then cured in an oven at 60°C for 10 minutes to form the  
dried matrix of peripheral region having a thickness of  
about 200 microns. The peripheral region obtained by this  
35       product is designated Intermediate Product A (IP-A).

          Ceraphil 31 (by Van Dyk/New Jersey), n-decyl alcohol,  
40       ethyl lactate and ethanol are mixed thoroughly at the weight  
ratio of 1:1:1:2 to form a homogeneous alcoholic enhancer  
system (AES). Dissolve excess amount of P4 in AES to form  
45       an oversaturated P4/AES solution. Carefully dispense 150  
microliter of P4/AES solution by a dispenser onto a piece of  
50       50 micron-thick heat-sealable (ethylene/vinyl acetate) mem-  
brane (EVA, 28% vinyl acetate, by 3M Co.) which was precast  
on the siliconized paper release liner. Quickly cover the  
55       dispensed P4/AES solution with a piece of drug-imper-  
meable/heat-sealable backing film (Scotch Pak 1109 by 3M

5 Co.). The central region of this biregional drug delivery  
10 system is then formed by thermally sealing the backing film  
to the EVA film by a specially designed heat seal machine.  
15 Sealing process was performed at 370<sup>0</sup>F and 50 psi for 1  
(one) second of dwell time. The central region (16.0 sq cm  
in size) obtained by this process is designated Intermediate  
20 Product B (IP-B).

To complete the fabrication of the biregional transder-  
mal drug delivery system, IP-A is carefully laminated onto  
25 the IP-B by a laminating device. The final dosage unit  
product (25.0 sq cm in size), is cut out by a die cutter.

30 The novel design of this dosage unit product allows the  
two drugs to be delivered simultaneously. P4 is delivered  
from the central region, while E2 is delivered from the  
35 peripheral region. In addition to variation of the formula-  
tion ingredients in each region, the daily delivery rate of  
each drug can be altered by changing the relative size of  
40 the surface area of the two regions. This dosage unit has  
the 16.0 and 7.50 sq cm of surface area for the central and  
45 peripheral regions, respectively, to allow desired amount of  
P4 and E2, respectively, to be delivered. In the in-vitro  
50 skin permeation study, this final product was found to give  
permeation rate of 44.88 and 0.31 mcg/sq cm/hr of P4 and E2,  
respectively, which can be translated into the daily  
55 delivery rate of 17.23 milligram of P4 and 55.8 mcg of E2.

5           Example 10

10           This example describes multi-region transdermal contra-  
15           ceptive delivery (mr-TCD) dosage units and methods for  
20           making them. The dosage units can be designed to deliver  
25           different contraceptive steroid hormones from different  
30           regions within a single dosage unit. Combination of a pro-  
35           gestin and an estrogen can be delivered transdermally from a  
40           single dosage unit of this system to achieve desired contra-  
45           ceptive efficacy. The dosage unit has a hormone-containing  
          layer having different regions in which different steroids  
          with/without skin permeation enhancers are contained. A  
          region can contain a progestin with enhancer(s) while  
          another region can contain an estrogen without enhancer(s)  
          or with different enhancer(s). If desired, a mr-TCD system  
          can have a region which contains no steroid hormones and no  
          skin permeation enhancer and which is used to segregate the  
          other hormone-containing regions. The location and the area  
          of each region in a mr-TCD system can vary and can be speci-  
          fically designed to control the release of hormones at opti-  
          mal rates to achieve greater contraceptive efficacy.

50           Factors that can be varied to control the amount or  
          ratio of amount of progestin and estrogen from such a system  
          include:

- 55           1. Area and area ratio of each region.  
          2. Hormone concentration in the polymer or polymer adhe-  
          sive which forms each region.

- 5           3.   Types of polymer or polymer adhesive which form each  
            region.
- 10          4.   Types of skin permeation enhancers incorporated in the  
            polymer or polymer adhesive.
- 15          5.   Amount of skin permeation enhancer(s) incorporated in  
            the polymer or polymer adhesive.
- 20          6.   Thickness of coating of each region.

25           FIG. 18 shows a cross sectional view of a dosage unit  
and top plan view of a three-region mr-TCD system. This  
system consists of the following elements:

- 30          A.   Low adhesion hormone-impermeable release liner.
- 35          B.   Central-region, which contains hormone with/without  
            skin permeation enhancers.
- 40          C.   Peripheral-region, which contains hormone with/without  
            skin permeation enhancers.
- 45          D.   Hormone-impermeable backing layer.
- 50          E.   Barrier region which contains no hormones nor skin  
            permeation enhancers.

55           The selection of which hormone (estrogen or progestin)  
to incorporate into which region (either central or peri-  
pheral) depends on therapeutic needs, formulation factors  
and fabrication procedures.

            If skin permeation enhancer is incorporated in the  
60          central region B along with a progestin, an estrogen can be  
incorporated in peripheral region C which contains no or

5 very little skin permeation enhancer. By such a configura-  
tion, the estrogen-containing peripheral region C can also  
10 serve as a peripheral adhesive ring which will help to main-  
tain adhesiveness of the whole mr-TCD on the application  
15 site of the skin. This configuration is especially useful  
in the situation in which the central region B is required  
to contain higher concentration of skin permeation enhancer  
20 in order to achieve desired skin permeation rate of proges-  
tin and thereby loses adequate adhesiveness. Therefore, as  
25 a general rule, the region which contains formulation that  
is more adhesive to the skin should be assigned as peri-  
pheral region.

30 The estrogens that can be used in this system include  
17-estradiol, ethinyl estradiol, and others described above.  
35 Progestins, such as levonorgestrel, norethindrone, and  
others described above, can be used with the estrogen used.  
Skin permeation enhancers of various types as described  
40 above, surfactants (anionic, cationic, non-ionic and  
zwitterionic types), and the combination of surfactants with  
45 straight long-chain alkanols, alkanoic acids or alkanoic  
acid esters, can be used in various concentrations in the  
central region of the mr-TCD system. Region E can be left  
50 as a trench or be filled with a material, such as a polymer  
or polymer adhesive, to prevent or to inhibit the inter-  
55 regional migration of hormones and/or skin permeation  
enhancers. The polymers used to construct this band can be  
selected from high-density polyethylene, polypropylene,

5 polystyrene, polyisobutylene, and other suitable materials.

10 On a piece of backing laminate (Scotch Pak 1109, 3M Co.), a layer of adhesive solution (Duro-Tak 80-1054, National Starch and Chemical Co.) is applied at the thick-  
15 ness of 200 microns. This adhesive solution contains 1% (W/W) estradiol (E2) and 10% (W/W) of n-decyl alcohol (n-DA). The coating of this E2/n-DA adhesive solution is  
20 applied to form the peripheral region C as shown in FIG. 18. Coating is performed by using a sophisticated Laboratory Coater (Type LTSV, Werner Mathis AG) which is equipped with  
25 specially-designed coating head and micrometers to control the thickness of coating. The peripheral coating C is then dried at 60°C for 10 minutes using Laboratory Dryer (Type LTF, Werner Mathis AG). This peripheral coating is here-  
30 after called intermediate product (I). Using the same equipment, a layer of 20% (W/W) polyisobutylene (Oppanol B80, BASF Co.) solution is coated onto the low-adhesion side  
40 of release liner (Scotch Pak 1022, 3M Co.) at the thickness of 600 microns. This coating is dried at 50°C for 5 minutes using the same drier used in the previous step. The dried  
45 coating of polyisobutylene polymer band is then laminated to the intermediate product (I) and then the release liner is removed to form the region D as shown in Figure 18. The  
50 product obtained is thereafter called intermediate product (II). Again, using the same coating equipment, a layer of Duro-Tak (80-1054, National Starch and Chemical Co.) adhe-  
55

5 sive solution containing 1% (W/W) of levonorgestrel, 10% of  
Span 20 (Sigma Chemical Co.), 10% propylene glycol (Fisher  
10 Scientific Co.) and 10% of lauric acid (Sigma Chemical Co.)  
are coated onto the intermediate product (II) at the thick-  
15 ness of 400 microns. The coating is dried at 60°C for 15  
minutes in the same drier used in the previous steps. After  
the drying is complete, the coating of the three regions is  
20 then covered with a release liner (Scotch Pak 1022, 3M Co.).  
The product obtained after this step of coating, drying and  
lamination processes consists of three concentric regions as  
25 shown in FIG. 18. The area ratio of region C over region B,  
in this case, is 1.25:1. The long-term (140 hours) in-vitro  
30 skin permeation rates of levonorgestrel and estradiol were  
found to be 0.52 ( $\pm 0.07$ ) and 0.20 ( $\pm 0.03$ ) mcg/sq cm/hr,  
35 respectively, when adult caucasian female cadaver skin was  
used in the in-vitro test procedure. If the area of region  
B is 5 sq cm (area of region C becomes 6.25 sq cm) a mr-TCD  
40 system of this configuration and size would be able to  
simultaneously deliver 62.4 ( $\pm 8.4$ ) mcg of levonorgestrel and  
45 30.0 ( $\pm 4.5$ ) mcg of estradiol per day. Therefore, ratio of  
daily delivery rate of levonorgestrel/estradiol is cal-  
culated as 2.08.

50 This example illustrates that by controlling the compo-  
sition of enhancers, drug loading, thickness of coating area  
of each region, the ratio of daily delivery rate of proges-  
55 tin/estrogen can be controlled by using the mr-TCD system  
described above.

5

10           The shape of the dosage units can be varied. The  
regions can be parallel strips or have other appropriate  
shapes and/or configurations.

15           Ethinyl estradiol or other estrogens can be used and  
the progestins described above can be used instead of 17-  
beta-estradiol and levonorgestrel, respectively.

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What is Claimed is:

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1. A transdermal dosage unit comprising:

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a. a backing layer which is impervious to the ingredients of the dosage unit;

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b. a reservoir layer which has a reservoir region in which there is dissolved in a liquid medium for transdermal absorption one or more pharmaceuticals which are present therein in the form of micro-reservoirs or a macroreservoir;

25

c. the absorption rate of said one or more pharmaceuticals being substantially constant for at least 24 hours and providing by transdermal absorption effective amounts thereof;

30

d. said reservoir region having an outer wall being a permeability-regulating polymer membrane which is substantially non-porous and which provides said substantially constant rate of transdermal absorption of said one or more pharmaceuticals; and

35

40

e. said dosage unit adapted to adhere to a subject using said dosage unit.

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2. A dosage unit of Claim 1 wherein the reservoir region has said pharmaceuticals present in the form of a macroreservoir region.

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3. A dosage unit of Claim 2 wherein the reservoir layer has an adhesive region which is separate from said macroreservoir region.

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4. A dosage unit of Claim 3 wherein the macroreservoir region has applied thereto an adhesive layer adapted to adhere said dosage unit to said subject.
5. A dosage unit of Claim 1 wherein said reservoir region said pharmaceuticals present in the form of microreservoirs.
6. A dosage unit of Claim 5 which further comprises a second region which provides adhesion to said subject.
7. A dosage unit of Claim 1 wherein said reservoir region has an adhesive region which is separate from said reservoir region and has a pharmaceutical dispersed therein in the form of microreservoirs.
8. A dosage unit of Claim 1 wherein said liquid medium is a biocompatible combination of miscible solvents.
9. A dosage unit of Claim 8 wherein one of said solvents is water.
10. A dosage unit of Claim 8 wherein the combination of miscible solvents comprise water and ethyl alcohol.
11. A dosage unit of Claim 1 wherein said liquid medium comprises a C<sub>3</sub>-C<sub>4</sub> alkane diol.
12. A dosage unit of Claim 2 wherein the solvent is propylene glycol.

5

13. A transdermal dosage unit comprising:

10

a. a backing layer which is impervious to the ingredients of the dosage unit;

15

b. a reservoir layer which is attached to said backing layer which has multiple regions, at least two of which in use contact the skin of a subject using said dosage unit, and provide transdermal absorption of one or more pharmaceuticals simultaneously.

25

14. A dosage unit of Claim 2, 5 or 13 wherein said pharmaceuticals are selected from hormonal steroids or combinations thereof.

30

15. A dosage unit of Claim 2 wherein at least one of said pharmaceuticals is 17-beta-estradiol.

35

16. A dosage unit of Claim 2, 5, 7 or 13 wherein said pharmaceuticals are anti-HIV pharmaceuticals.

40

17. A dosage unit of Claim 2, 5, 7 or 13 wherein said pharmaceuticals are a combination of pharmaceuticals providing combination treatment.

45

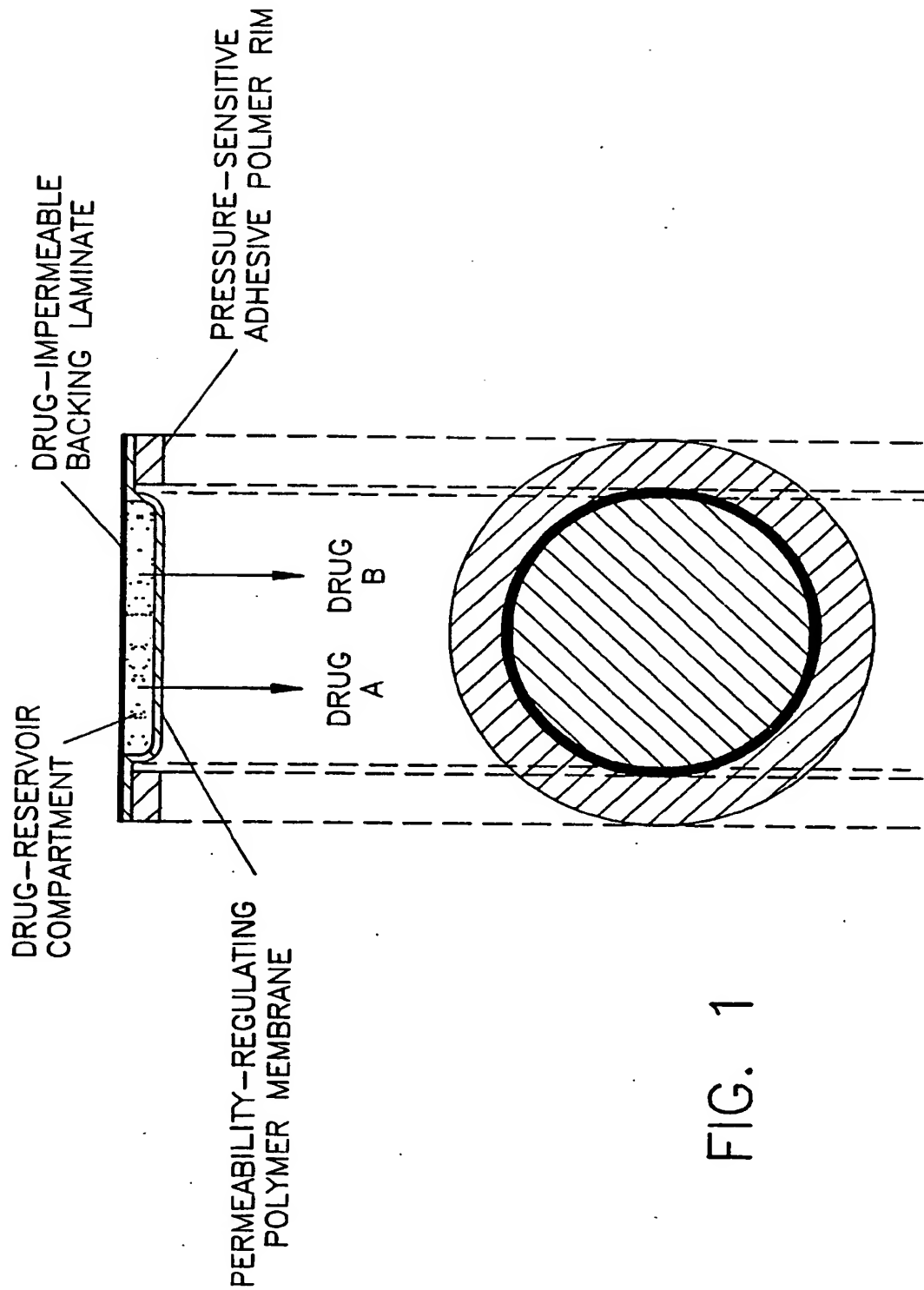
18. A dosage unit of Claim 2, 5, 7 or 13 wherein said pharmaceuticals are a combination of a diuretic and an antihypertensive pharmaceutical providing combination therapy.

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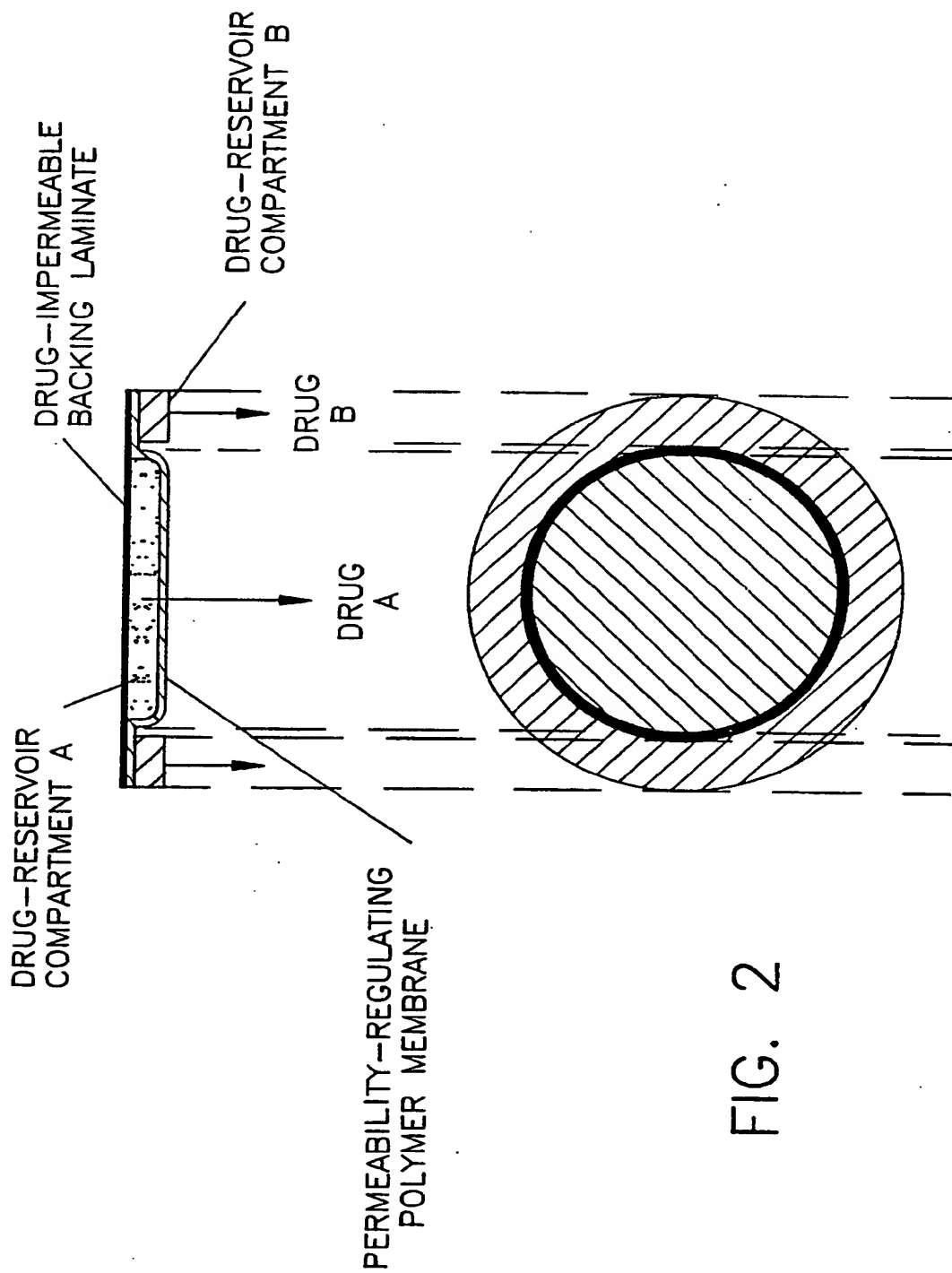
- 5           19. A dosage unit of Claim 2, 5, 7 or 13 wherein said  
dosage unit has an effective amount of one or more  
10           transdermal absorption enhancers.
- 15           20. A dosage unit of Claim 19 wherein said transdermal  
absorption enhancer is selected from the group consist-  
ing of long chain alkanoic acids, long chain alkanols,  
20           alkyl esters of lactic acids and combinations thereof.
- 25           21. A dosage unit of Claim 1 wherein membrane is a substan-  
tially non-porous ethylene/vinyl acetate film.
- 30           22. A process for transdermally administering one or more  
pharmaceuticals by use of a dosage unit of Claim 2, 5,  
7 or 13.

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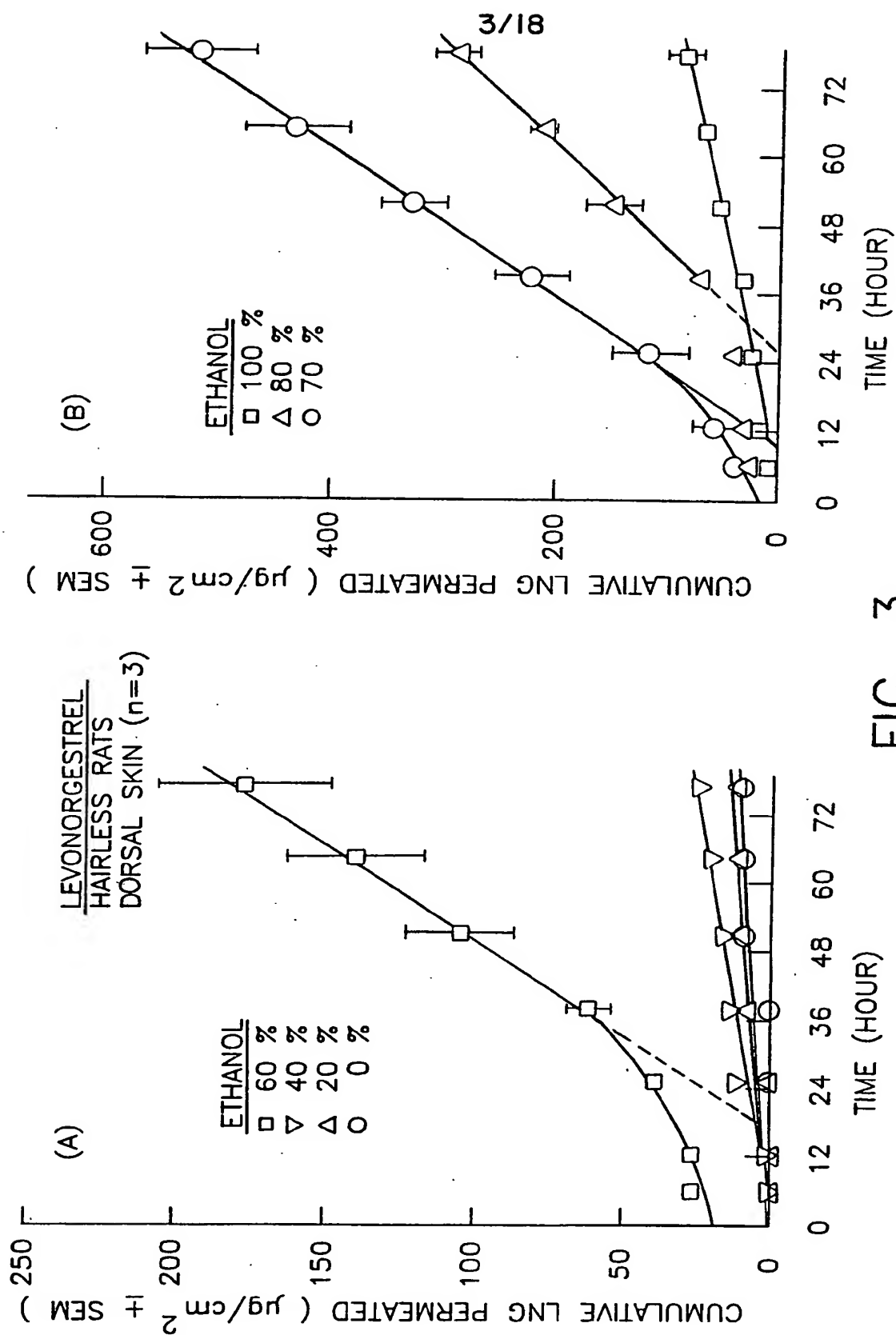


FIG. 3

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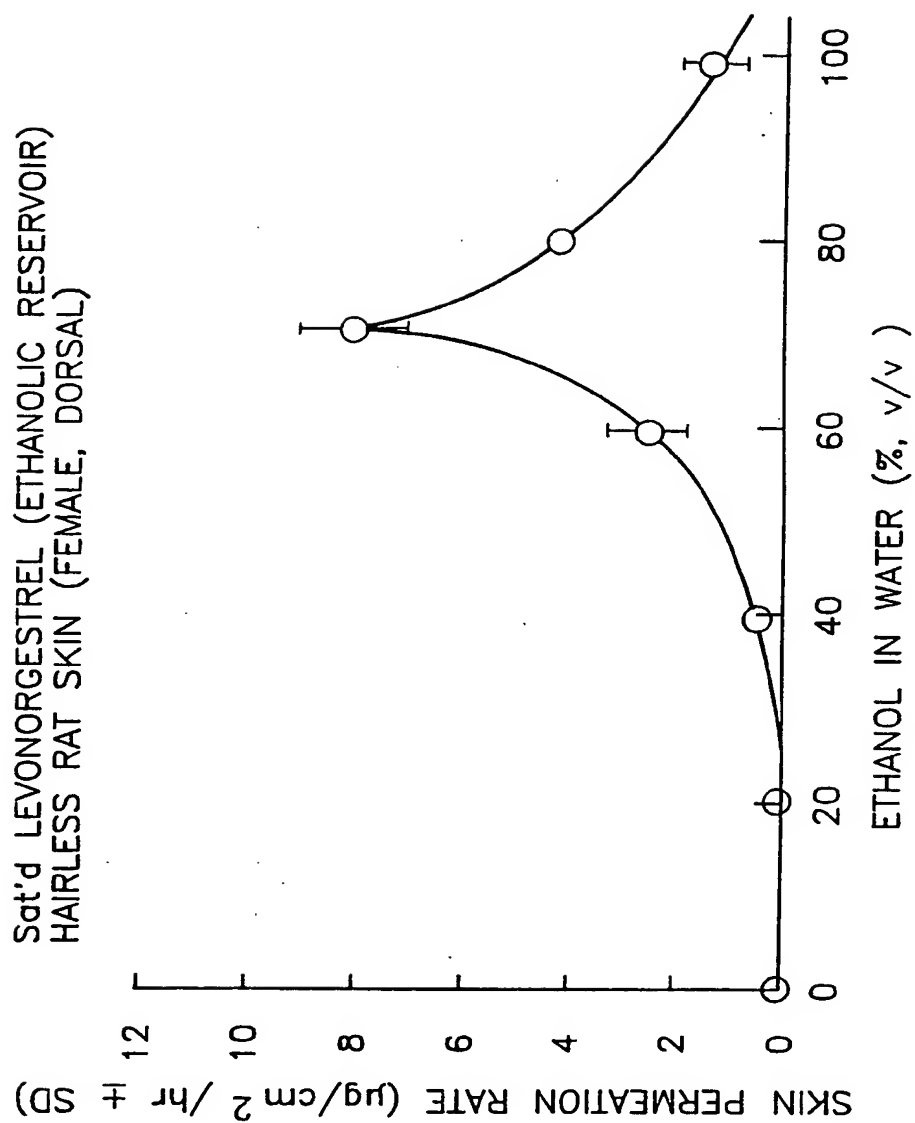


FIG. 4

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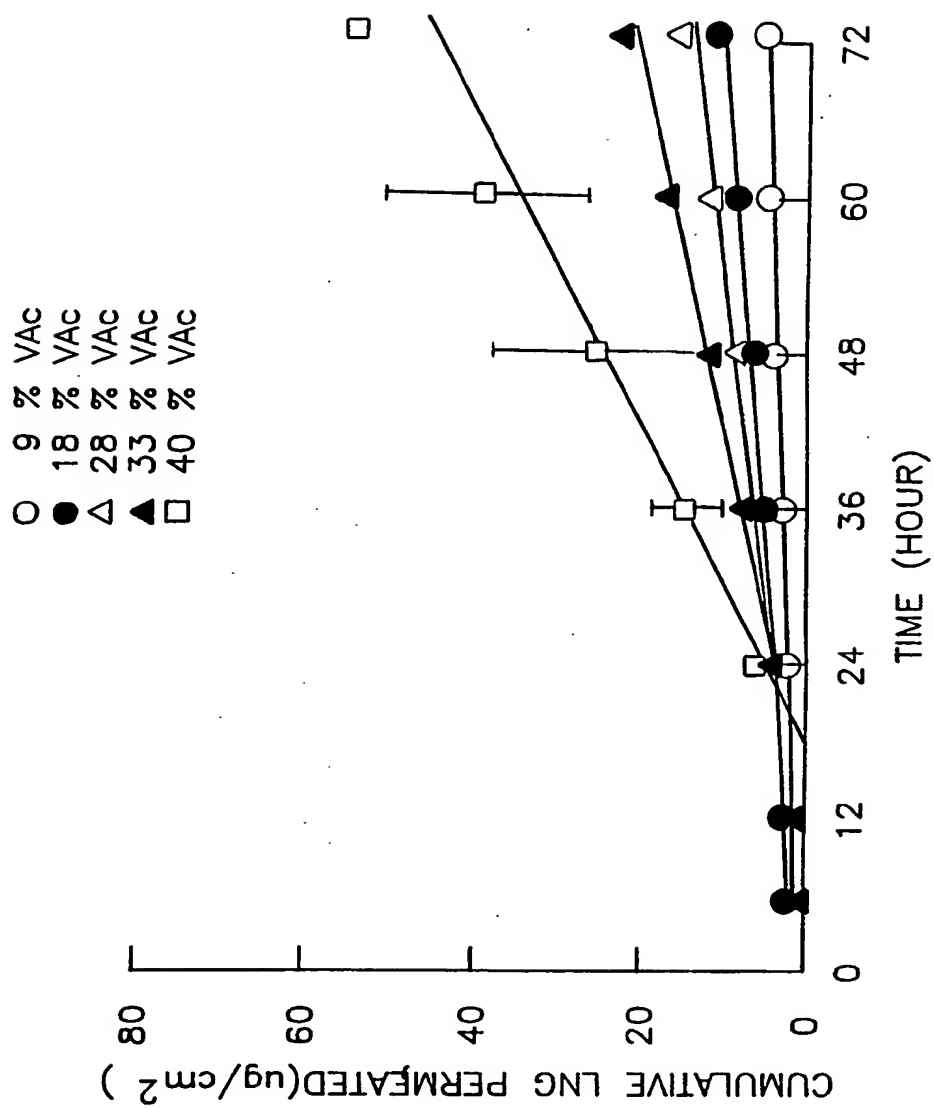


FIG. 5

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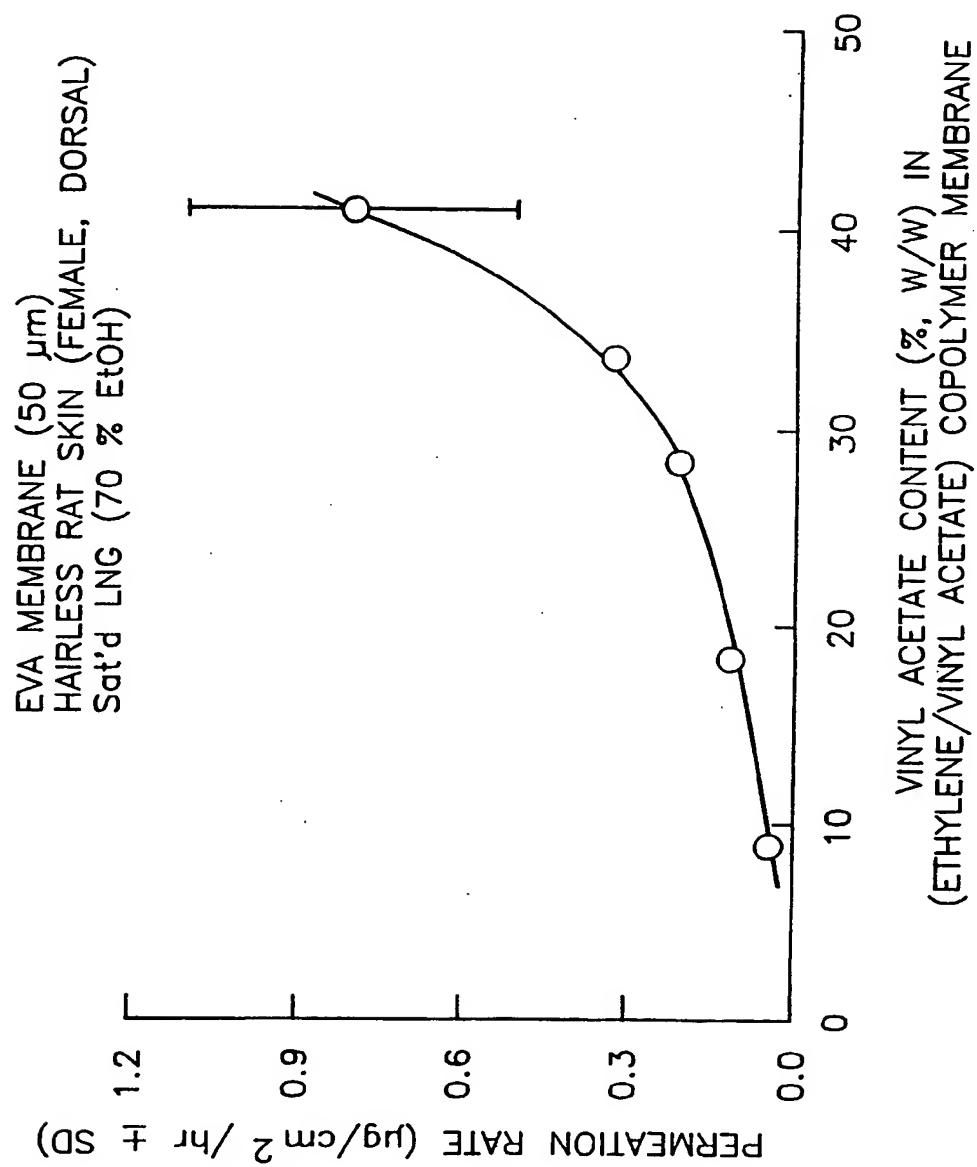


FIG. 6

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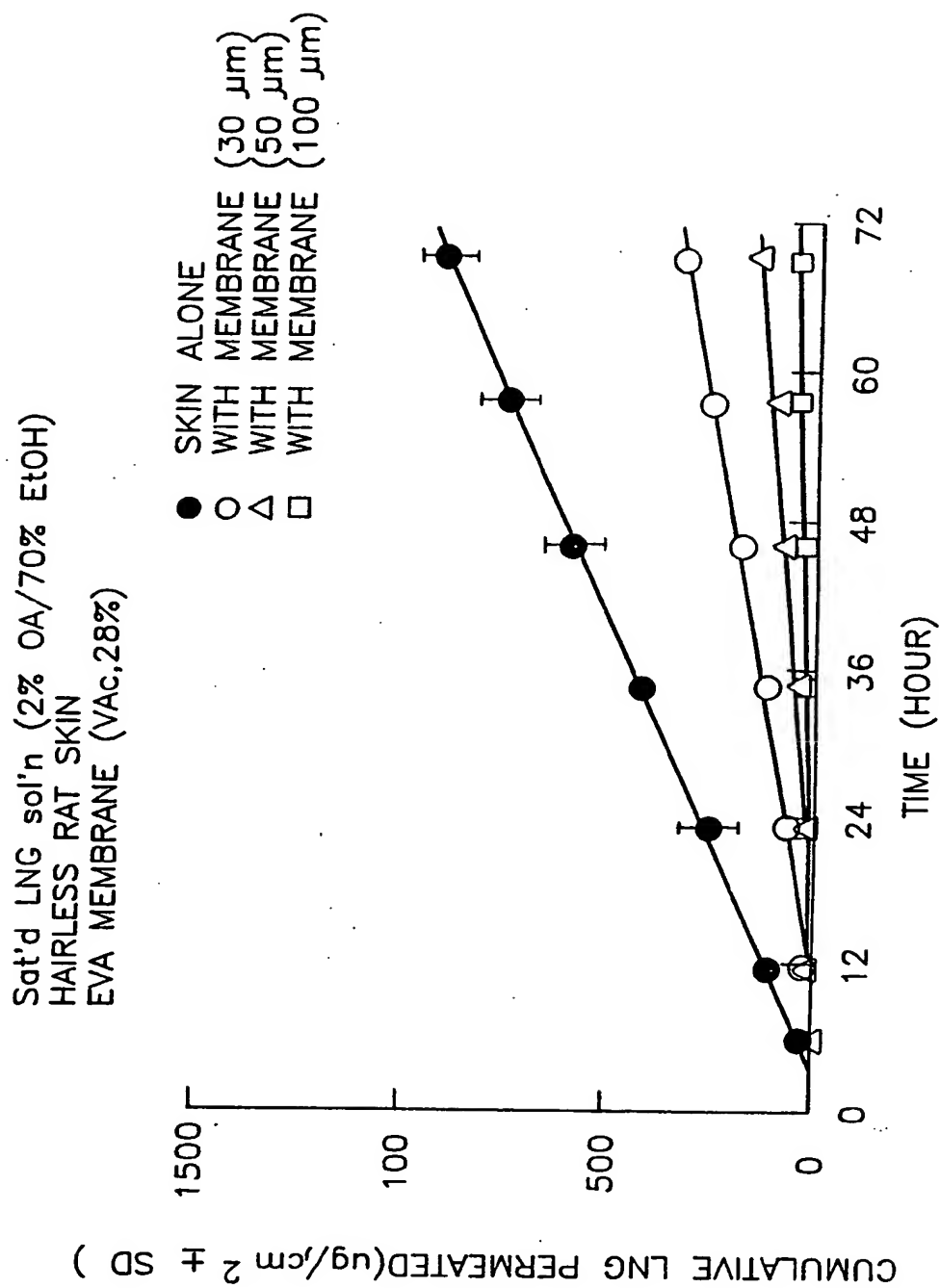


FIG. 7

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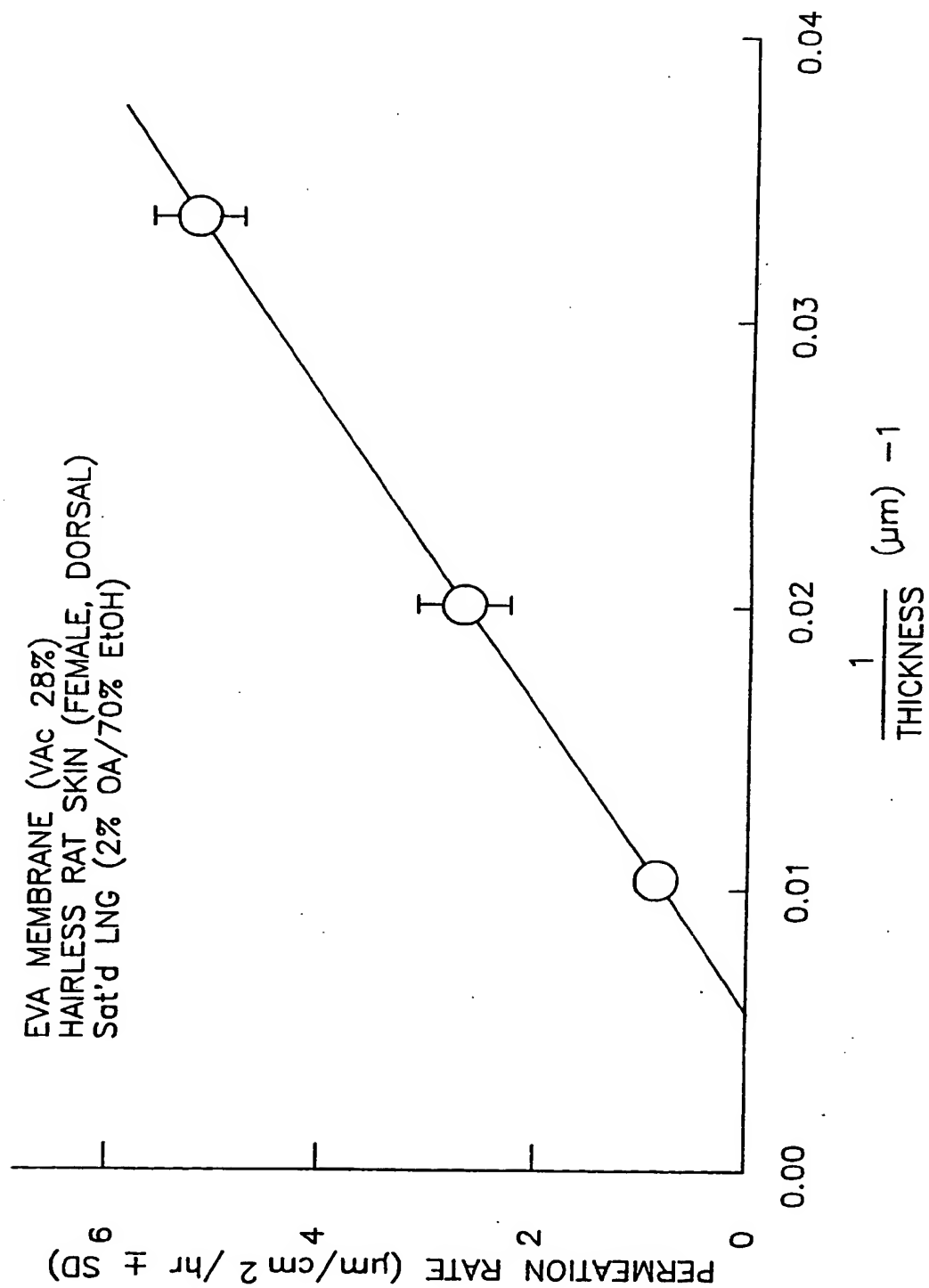


FIG. 8

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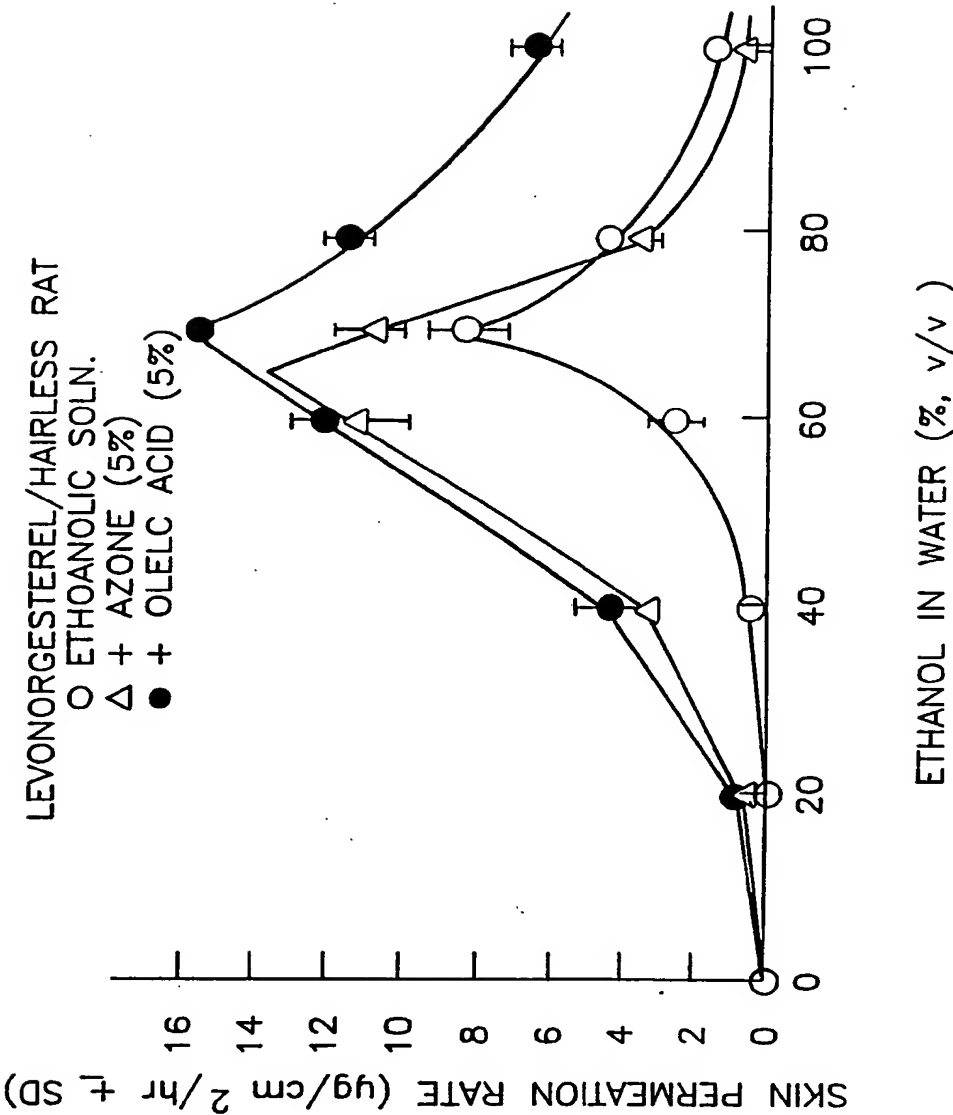


FIG. 9

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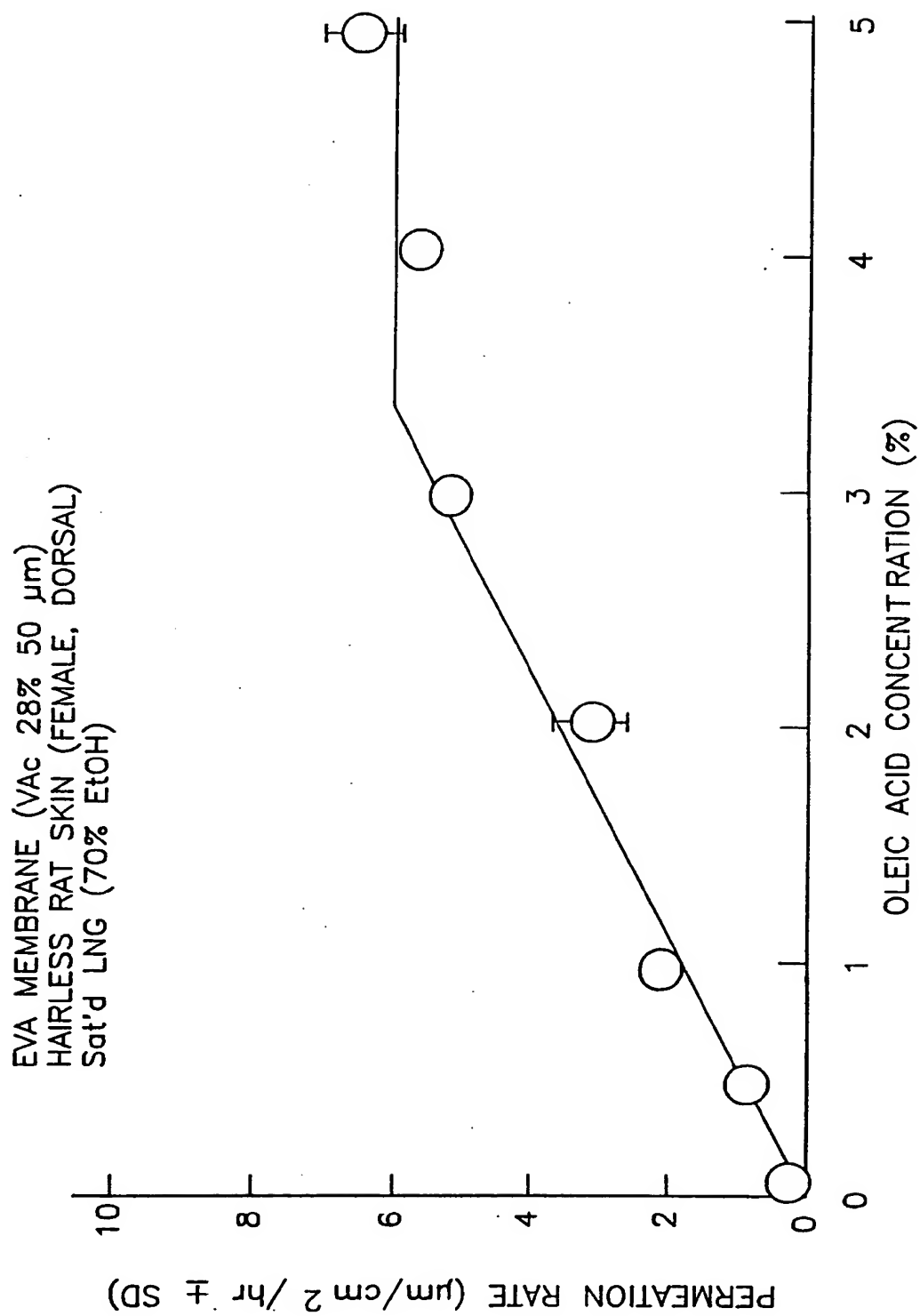


FIG. 10

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EVA MEMBRANE (VAc 28% 50  $\mu\text{m}$ )  
HAIRLESS RAT SKIN (FEMALE, DORSAL)  
Sat'd LNG (2% OA/70% EtOH)

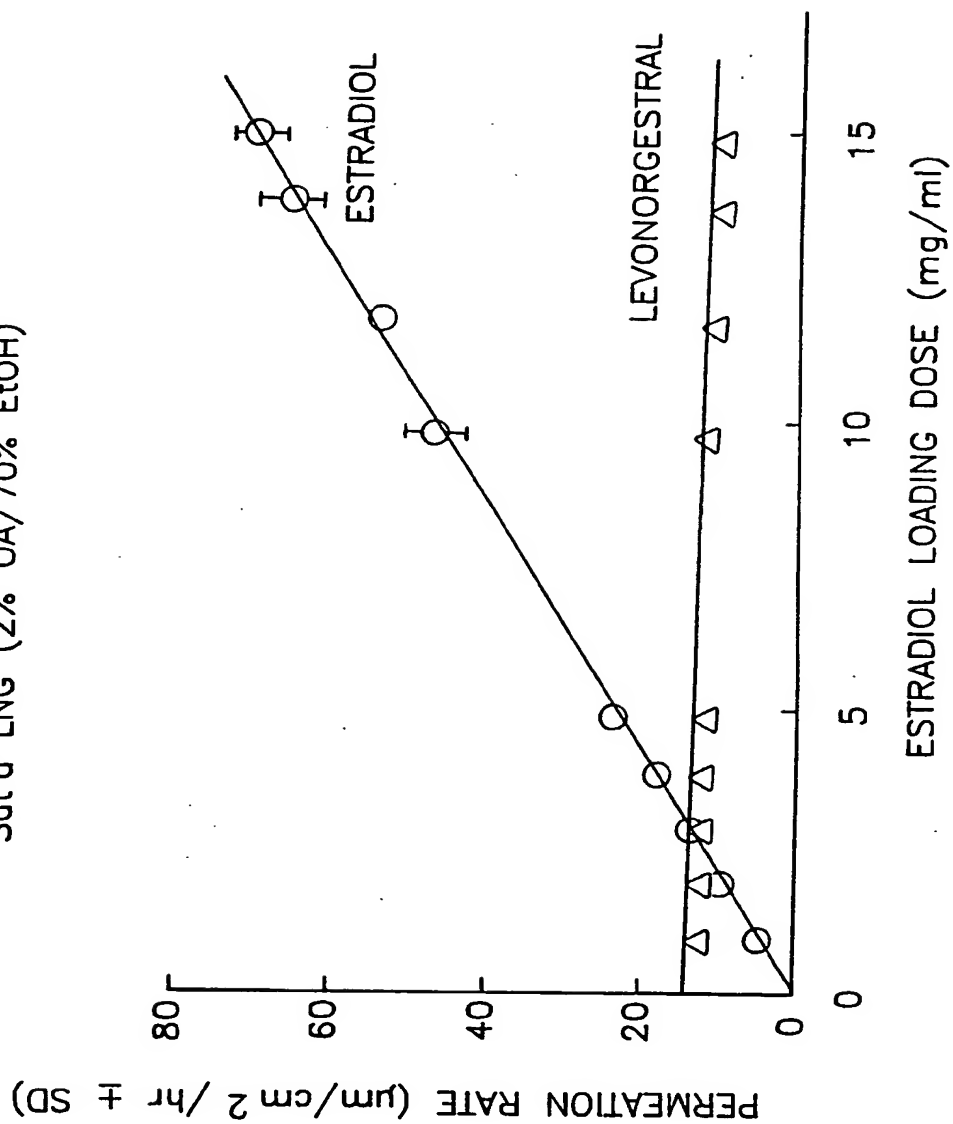


FIG. 11

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EVA MEMBRANE (VAc 28% 50  $\mu$ m)  
HAIRLESS RAT SKIN (FEMALE, DORSAL)  
Sat'd LNG (2% OA/70% EtOH)

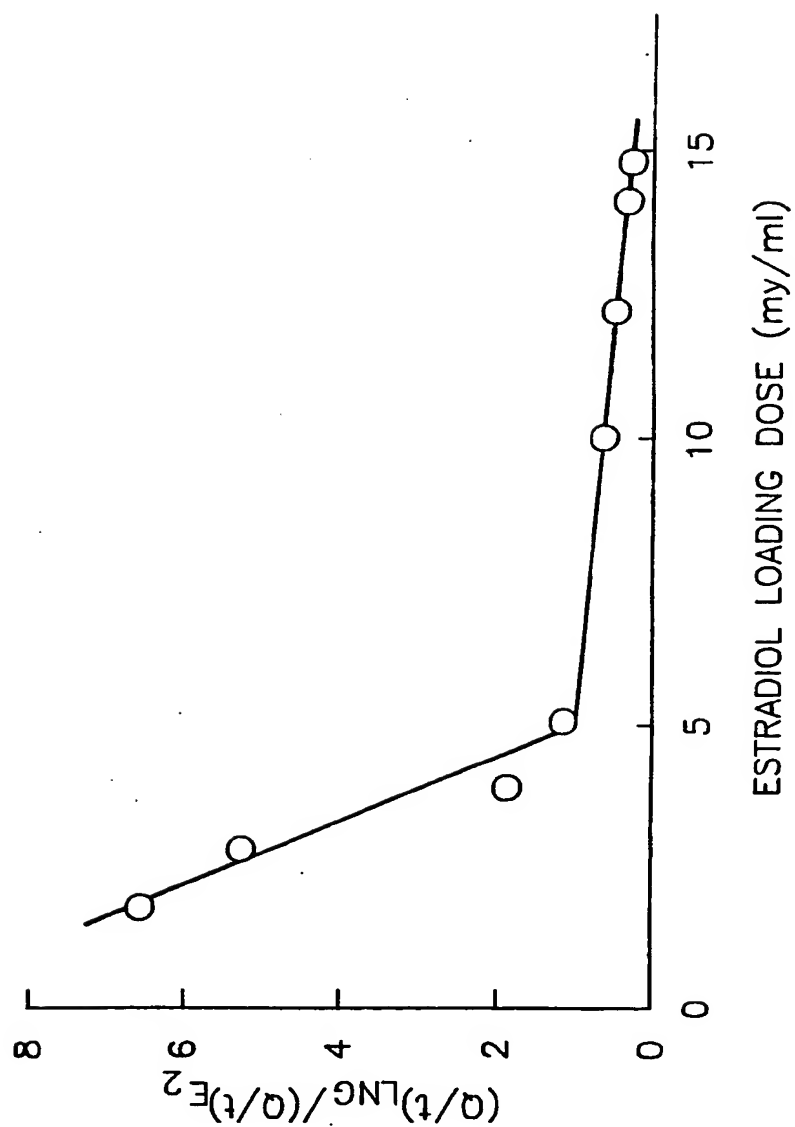


FIG. 12

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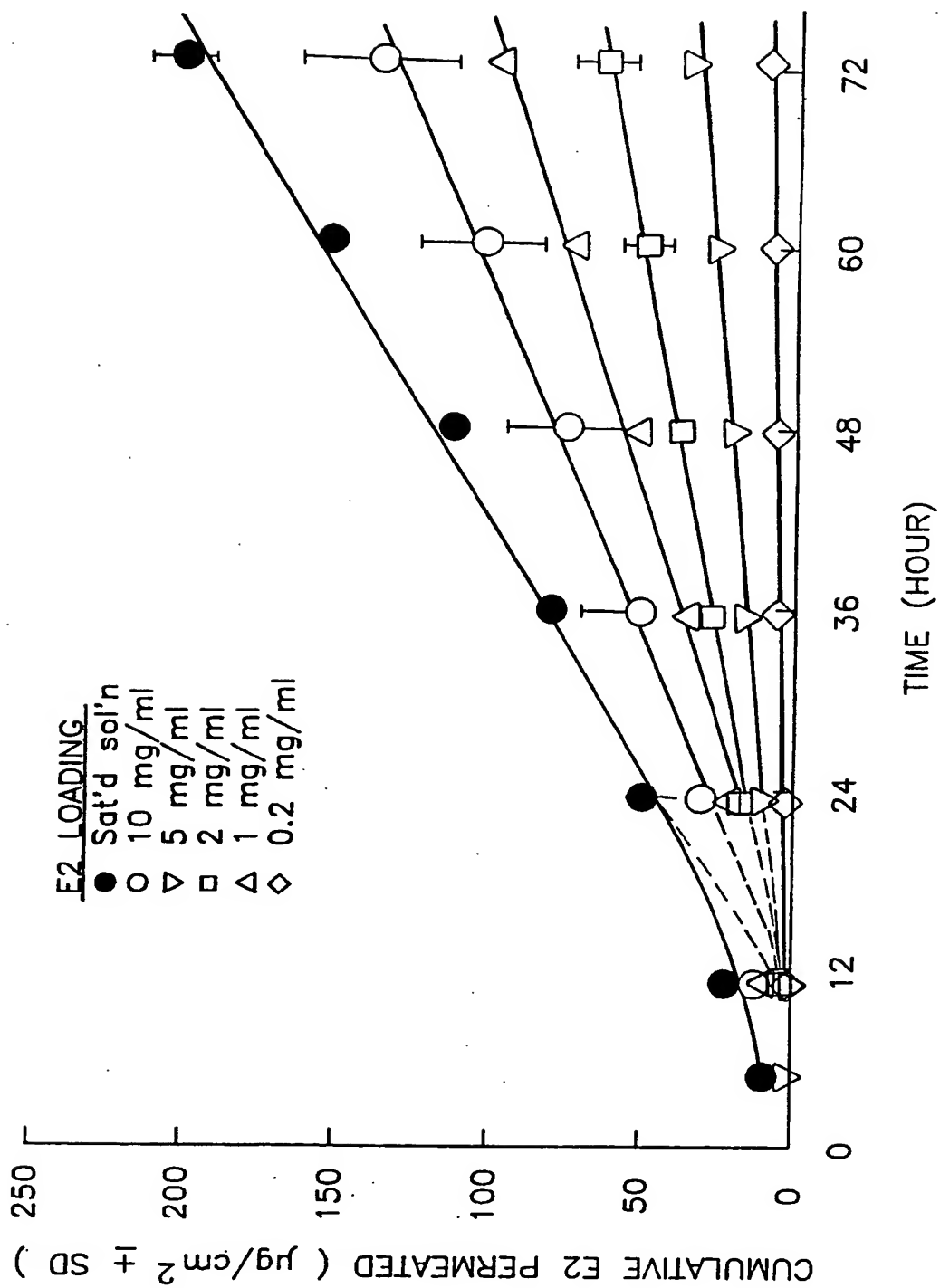


FIG. 13

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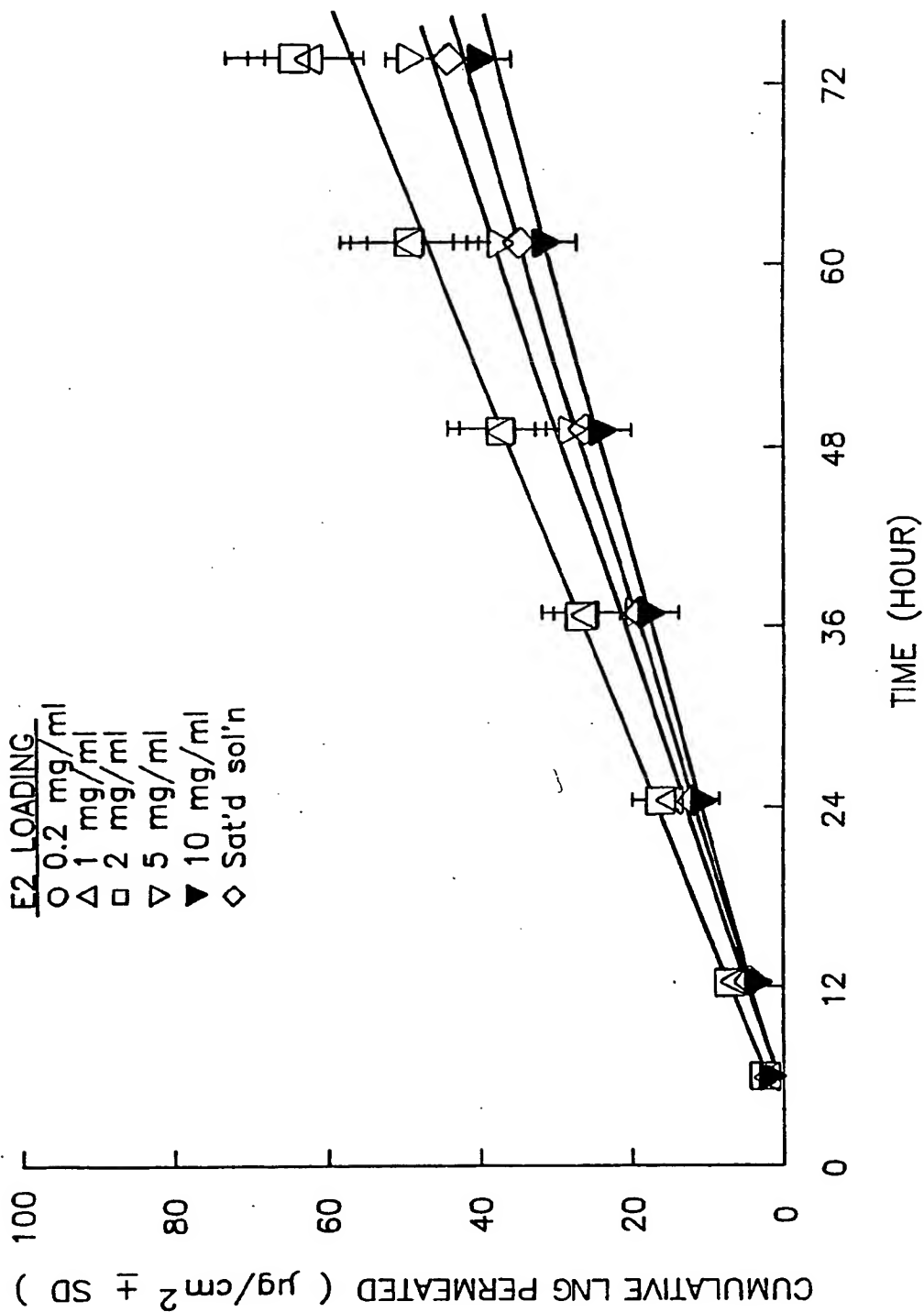


FIG. 14

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EVA MEMBRANE (VAc 28% 50  $\mu\text{m}$ )  
Sat'd LNG (2% OA/70% EtOH)  
HUMAN CADAVER SKIN (FEMALE, 34YRS)

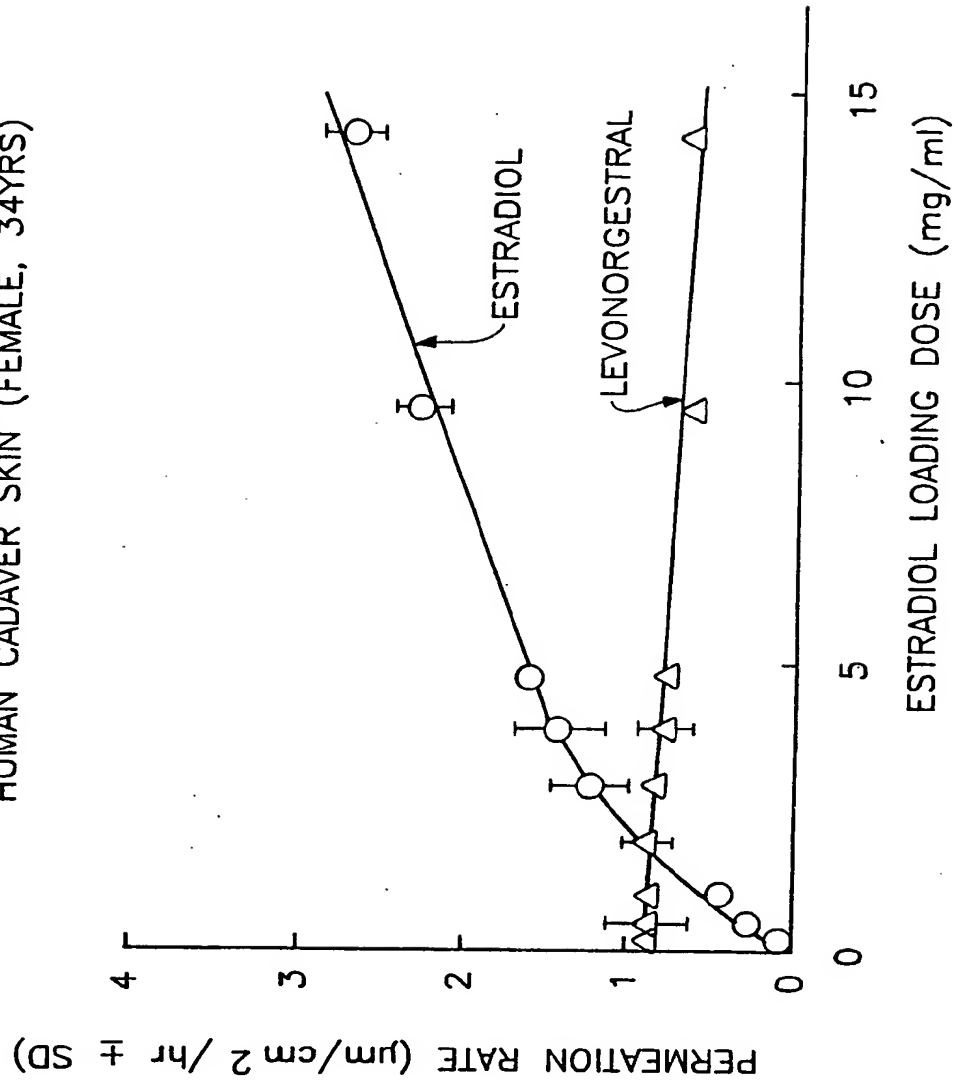


FIG. 15

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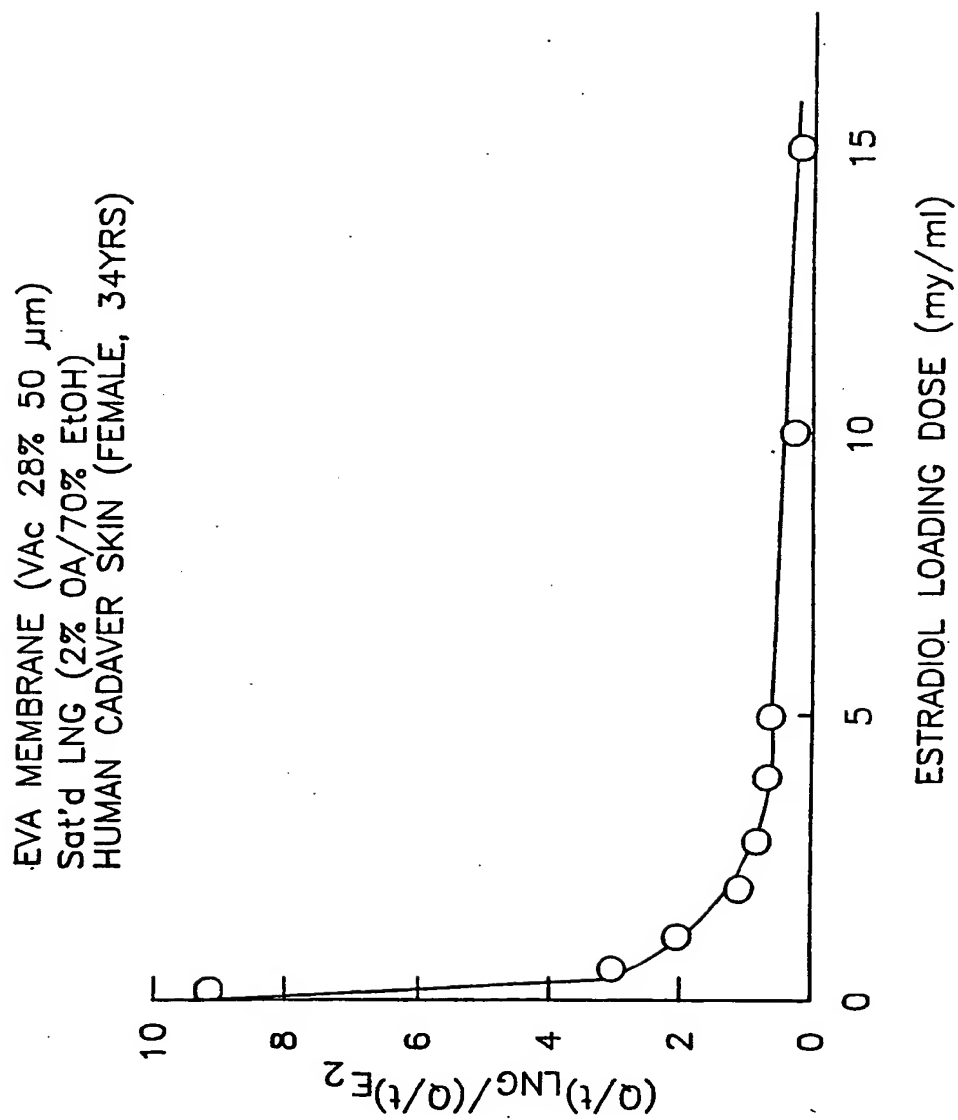


FIG. 16

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LNG/EtOH (70%)(21.84  $\mu\text{g}/\text{cm}^2$  /DAY)  
EVA MEMBRANE (28% VAc; 50  $\mu\text{m}$ )  
E<sub>2</sub> / POLYACRYLATE (24.36  $\mu\text{g}/\text{cm}^2$  /DAY)

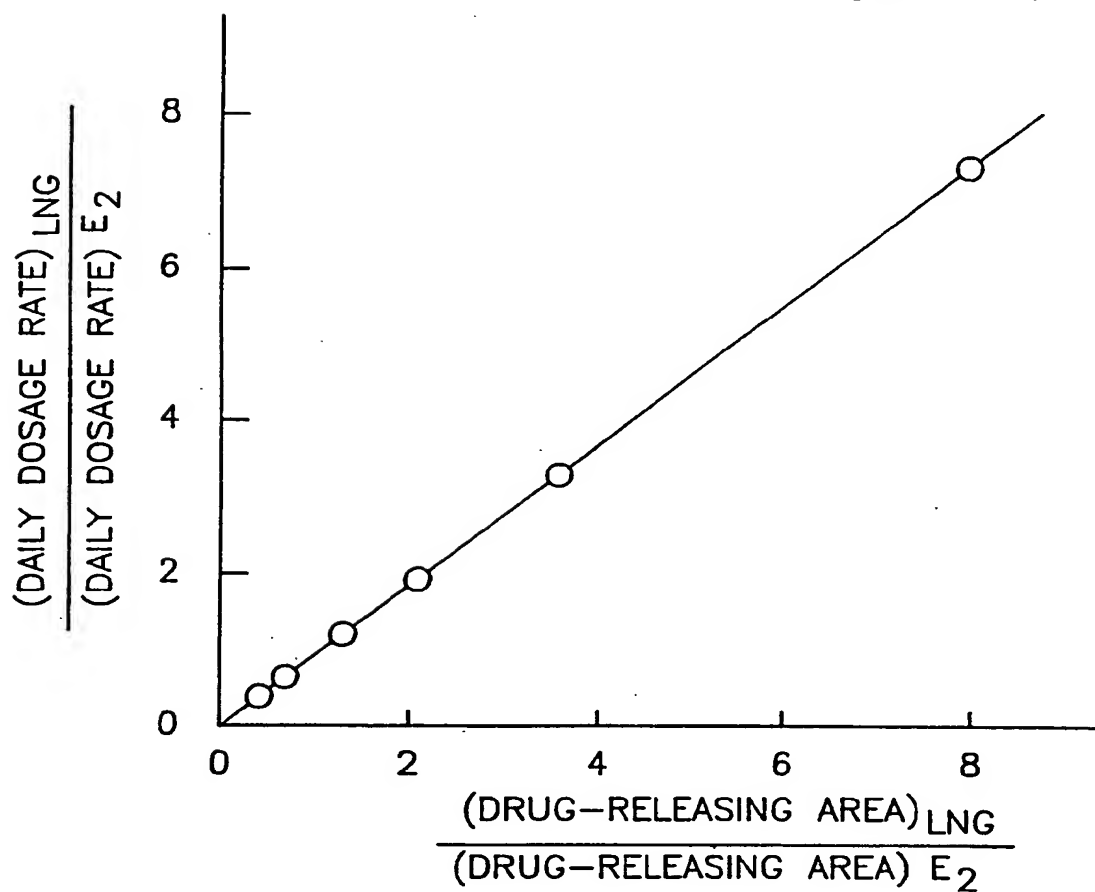


FIG. 17

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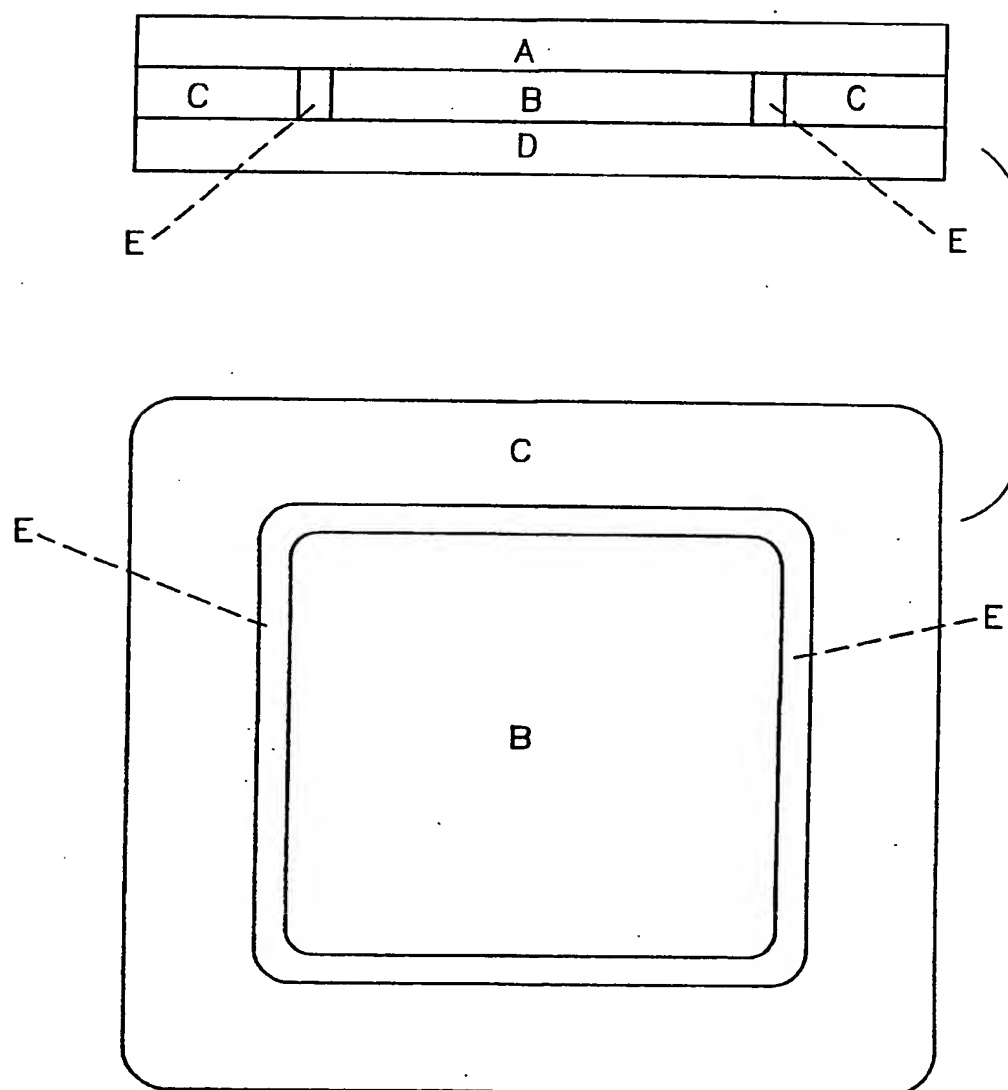


FIG. 18

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## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US93/08714

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(5) :A61F 13/02, 13/00

US CL :424/448, 449

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/448, 449

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim N .
A	US, A, 4,818,540 (CHIEN ET AL) 04 APRIL 1989, see entire document.	1-22
A	US, A, 5,023,084 (CHIEN ET AL) 11 JUNE 1991, see columns 8-18.	1-22

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* Special categories of cited documents:	*T	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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*P* document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

26 OCTOBER 1993

Date of mailing of the international search report

15 DEC 1993

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Washington, D.C. 20231

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